Metronidazole in the Treatment of Chronic Radiation Proctitis: Clinical Trial

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Aim. To evaluate the effectiveness of metronidazole in combination with corticosteroids in enema and mesalazine (5-aminosalicylic acid) in comparison with the same protocol with out metronidazole in the treatment of chronic radiation proctitis.

Methods. Sixty patients with rectal bleeding and diarrhea were randomly divided into two groups. Patients in the first group were treated with metronidazole (3x400 mg orally per day), mesalazine (3x1 g orally per day), and betamethasone enema (once a day during 4 weeks). Patients in the second group were treated with mesalazine and betamethasone enema, but without metronidazole. The efficacy of metronidazole was assessed on the basis of rectal bleeding, diarrhea, and rectosigmoidoscopy findings in all patients.

Results. The incidence of rectal bleeding and mucosal ulcers was significantly lower in the metronidazole group, 4 weeks (p=0.009), 3 months (p=0.031), and 12 months (p=0.029) after therapy. There was also a significant decrease in diarrhea and edema in the metronidazole group, 4 weeks (p=0.044), 3 months (p=0.045), and 12 months (p=0.034) after treatment.

Conclusion. Metronidazole in combination with mesalazine and betamethasone enemas successfully treats rectal bleeding and diarrhea in chronic radiation proctitis.

Key words: betamethasone enema; diarrhea; flubenisolone; mesalazine; metronidazole; oncology; radiation; proctitis; prostatic neoplasms; radiology; radiotherapy

Irradiation therapy is an accepted method in the treatment of abdominal and pelvic, especially gynecological and urological malignant disease. Radiation-induced proctitis is a frequent consequence of external radiotherapy for prostatic carcinoma. The symptoms include diarrhea, rectal bleeding, and pain, which develop after a latency of several weeks, months, or many years following the radiation therapy (1.2). The prevalence of radiation-induced proctitis due to prostatic carcinoma treatment varies from 2% to 20% (3). Total doses of irradiation to the prostate up to 70 Gy were associated with a significant increase in the incidence of radiation proctitis (4).

Traditionally, a variety of treatment modalities have been tried for radiation-induced proctitis, with variable and inconsistent success (5). These include anti-inflammatory agents (6), topical steroid solutions (7), bipolar electrocoagulation (8), hyperbaric oxygen (9), laser application (10), formalin-soaked gauze (11,12), and short-chain fatty acids enema (13). The aim of this study was to evaluate the effectiveness of metronidazole in combination with corticosteroids in enema and oral mesalazine 5-aminosalicylic acid in the therapy of chronic radiation proctitis.

Patients and Methods

Patients

Sixty patients with chronic radiation proctitis and cytologically proven prostatic carcinoma staged according to the TNM classification from the UICC 1978 (14) as T2N0M0 stage, were assigned to receive either a combination of metronidazole, mesalazine, and corticosteroids in enema, or mesalazine and corticosteroids without metronidazole. Patients were allocated into 2 groups according to the date on which their treatment began: those starting the treatment on even dates were included in the first group, whereas those starting the treatment on odd dates were included in the second group.

The study, approved by the Hospital ethical committee, began in October 1990. The last patient was accrued in October 1997. The patient’s characteristics are shown in Table 1. All the patients had histologically proved chronic radiation proctitis.
proctitis and gave in formed consent to the study. No pa tients required blood trans fusion before treat ment.

Prostatic carci noma was diag nosed by digital ex amina tion, rectal ultrasound, cy to logical function, and the prostate specific an ti gen (PSA) test. The stage of the tumor was deter mined first by digital rectal ex amina tion and then by a CT scan.

All patients were irradiated with linear accelerator us ing an 8 MV photon beams. The treat ment schedule was 5 frac tions per week with a daily dose of 2.0 Gy for a mean tal dose of 68 Gy in over all treat ment time from 5.5 to 6.5 weeks. The mean from tal field size was 12x12 cm, and the mean lat eral field size was 10x16 cm. The ir radia tion was per formed in a 3-field tech nique and a shrink age field was used in all pa tients after 50 Gy with a field size of 9x9 cm. There was no difference in the radiotherapy between the two treat ment arms.

Me di um in ter val from the last r adia tion dose to the study was 12.2 months (range 10 to 16 months).

Diagnostic Criteria of Chronic Radiation Proctitis

All pa tients under went a com plete patient his to ry ex amination and labora tory analy sis (red blood cell count, white blood cell count, ur in e, aspartate am ino trans ferase, alanine am ino trans ferase, coagulation tests, creatinine), stool ex amination (cul ture for Clostridium difficile, Staphylo co cus, Campylobacter, Salmonella, Shigella, and examina tion for ova and parasites), digital ex amination, an oscopy, rectosigmoidoscopy, contrast study of the small bowel, bar i um enema, and en doanal ultra sound. Each of the pa tients suf fered from chronic symp to ms (rectal bleed ing and di ar rhea). Apart from sec ond ary anemia, all other lab or a tory tests re sults were within the nor mal range. An oscopy showed muscosal hyperemia, edema, small ulcers, and blood and sm ele in the anal ca nal. Rectosigmoidoscopy re vealed in tense ery the ma, edema, friabil ity, ulcer a tions, and tel engiectasia up to 10 cm from the anal verge. Changes were more in tense on the an terior wall of the rectum. In all cases, the diag no sis was es tab lished by histological ex am i na tion of the rec tal mu cosa, which showed an ische mia caused by ob li terative endo arteritis and fibrosis (1), although most authors rarely con sider biopsy of rec tum as an ac cept able method, since it may pre cip i tate ul cer a tion and fistula for ma tion (15).

Treat ment of Chronic Radiation Proctitis

Pa tients in the metronidazole group were treated with metronidazole (Medazol, Belupo, Kopri Nina, Croatia) 3x400 mg orally per day, mesalazine (5-aminosalicylic acid; Salofalk, Dr. Falk Pharma, Freiburg, Ger many) 3x1 g orally per day, and betamethasone enema (Betnesol, Glaxo-Wellcome, Hamburg, Germany) once a day during 4 weeks. The group without metronidazole was treated with mesalazine and betamethasone enema the same way as the first group during 4 weeks.

As sess ment of the Proctitis

All pa tients were given a cal en dar and in struc ted to record every change con nected with med i ca tions they took, de tails of bowel ac tion (num ber of bowel move ments, am ount and fre quency of hematochezia), and use age of any other med i ca tion in ad di tion to the drugs un der in vesti gation. Ob jective patient re sponse was doc u mented by rectal bleed ing score (Ta ble 2) and di ar rhea score (16). The pa tients were scored the same way be fore and af ter treat ment. The same phy si a tran inter viewed pa tients once a week during the treat ment pe riod. After 4 weeks of treat ment, the therapy was dis con tin ued. During the first year, the pa tients were re ex am ined for recurrence of symp toms every 3 months. After that period, con trol ex amination was per formed every 6 months. Ad vers e ac tions (skin rash, nau sea, or vom iting) that oc curred dur ing the treat ment were con sidered treat ment tox icity. Re ap pear ance of symp toms in pa tients who were symp tom-free for at least 3 months after treat ment was con sid ered a recur rence and the same therapy was reapplied for an addi tional 4-week period.

Per sistan ce of any symp tom 4 weeks after the begin ning of the therapy was sim i lar to the other pa tients, and the therapy was dis con tin ued. The lon gest fol low-up pe riod after 4 weeks of treat ment was 3 years, whereas the short est one was 2 years.

Statis ti cal Anal y sis

Differences in categ or ical vari ables be tween groups were tested with Fisher’s ex act test.

Results

None of the pa tients were ex cluded due to the intoler ance of therapy or adverse re ac tions to the med ications. At the begin ning of treat ment and during the con trol ex am i na tion pe riod, none of the 60 pa tients was pos itive for Clostridium difficile, Staphylo co cus, Campylobacter, Sal mo nella, Shigella, ova, or para sites. Barium enema and small bowel follow-through contrast study did not show changes in other parts of large and/or small in tes tine. Endoanal ultrasound did not show the dam age of the internal anal sphincter.

Rectal Bleeding

After 4 weeks of the treat ment, there was a sta tis tically sig nif i cant dif fer ence in the oc cur rence of rectal bleed ing be tween the group with metro ni dazole and group with out metronidazole (Ta ble 3). Sim ilar re su lts were ob served 12 and 12 months af ter the cessation of metronidazole therapy (Ta ble 4). Two years af ter the treat ment, the in ci dence of rectal bleeding was sim ilar in both groups.

Diarrhea

A sta tis ti cally sig nif i cant dif fer ence in the oc cur rence of di ar rhea be tween group with metro ni dazole and group with out metronidazole was also doc u mented after 4 weeks of treat ment (Ta ble 3). Sim ilarly, de crease in the in ci dence of se ver ity of di ar rhea was ob served after 3 and 12 months.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment with mesalazine and betamethasone (control group)</th>
<th>Treatment with mesalazine, betamethasone, and metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (64–76)</td>
<td>68 (62–74)</td>
</tr>
<tr>
<td>Treatment time (weeks)</td>
<td>5.8 (5.2–6.3)</td>
<td>6.0 (5.5–6.5)</td>
</tr>
</tbody>
</table>

*Total radiation dose was 68 Gy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Rectal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no change in bowel habits (normal)</td>
<td>no blood in stool</td>
</tr>
<tr>
<td>1</td>
<td>small increase in frequency; soft stools</td>
<td>stool covered with blood</td>
</tr>
<tr>
<td>2</td>
<td>more pronounced increase in frequency; loose stools</td>
<td>stool mixed with blood</td>
</tr>
<tr>
<td>3</td>
<td>considerable increase in frequency and watery stools</td>
<td>only blood</td>
</tr>
</tbody>
</table>

Table 1. Characteristics (median, range) and treatment details in patients with chronic radiation proctitis

Table 2. Assessment score for diarrhea and rectal bleeding
in both groups (Table 4). After 24 months of treatment, no statistically significant difference in the occurrence of diarrhea between the group treated with metronidazole and the control group with out metronidazole was found.

Rectosigmoidoscopy

The incidence of mucosal ulcers was significantly lower in the group treated with metronidazole than in the group without metronidazole treatment 4 weeks after treatment (Table 3). Similar results were observed after 3 and 12 months of treatment (Table 4).

After 4 weeks of treatment, there was a statistically significant difference in the occurrence of the erythema/edema between the group treated with metronidazole and the group without metronidazole treatment (Table 3). Similar results were observed after 3 and 12 months of therapy (Table 4).

After 24 months of treatment, there was no statistically significant difference in the occurrence of mucosal ulcers and erythema/edema between the two groups (Table 4).

Table 3. Incidence and severity of diarrhea, rectal bleeding, and endoscopy findings before and four weeks after therapy in patients with chronic radiation proctitis

<table>
<thead>
<tr>
<th>Parametar</th>
<th>Before</th>
<th>After 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>metronidazole</td>
<td>control</td>
</tr>
<tr>
<td>Symptom score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rectal bleeding 0-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-3</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>diarrhea 0-1</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>2-3</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Rectosigmoidoscopy for rectal mucosa:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no erythema/erythema</td>
<td>15/15</td>
<td>13/17</td>
</tr>
<tr>
<td>no ulcers/ulcers</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td>no teleangiectasia/teleangiectasia</td>
<td>0/30</td>
<td>0/30</td>
</tr>
</tbody>
</table>

*Pa tients in the metronidazole group (n=30) were treated with metronidazole, mesalazine and betamethasone enema and those in the control group (n=30) with mesalazine and betamethasone.

*Not tested.

Table 4. Incidence and severity of diarrhea, rectal bleeding, and endoscopy findings 3 months, and 1 and 2 years after therapy in patients with chronic radiation proctitis

<table>
<thead>
<tr>
<th>Parametar</th>
<th>After 3 months</th>
<th>After 1 year</th>
<th>After 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>metronidazole (n=27)</td>
<td>control (n=18)</td>
<td>p</td>
</tr>
<tr>
<td>Symptom score:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rectal bleeding 0-1</td>
<td>26</td>
<td>13</td>
<td>0.031</td>
</tr>
<tr>
<td>2-3</td>
<td>1</td>
<td>5</td>
<td>0.031</td>
</tr>
<tr>
<td>diarrhea 0-1</td>
<td>25</td>
<td>12</td>
<td>0.045</td>
</tr>
<tr>
<td>2-3</td>
<td>2</td>
<td>6</td>
<td>0.045</td>
</tr>
<tr>
<td>Rectosigmoidoscopy for rectal mucosa:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no erythema/erythema</td>
<td>25/2</td>
<td>12/6</td>
<td>0.045</td>
</tr>
<tr>
<td>no ulcers/ulcers</td>
<td>26/1</td>
<td>13/5</td>
<td>0.031</td>
</tr>
<tr>
<td>no teleangiectasia/teleangiectasia</td>
<td>0/27</td>
<td>0/18</td>
<td>N.T.</td>
</tr>
</tbody>
</table>

*Pa tients in the metronidazole group were treated with metronidazole, mesalazine and betamethasone enema and those in the control group with mesalazine and betamethasone.

*Not tested.

Teleangiectasieae were found in all patients from both groups. After the treatment, there was no difference in incidence of teleangiectasia in both groups. We observed prolonged healing and long-lasting ulcer on the site of biopsy in all patients, and did not perform biopsies at control rectosigmoidoscopies.

Discussion

In our patient series, the use of metronidazole in combination with mesalazine and corticosteroid enemas in the treatment of radiation proctitis significantly decreased rectal bleeding and mucosal ulcerations, as assessed by rectosigmoidoscopy.

This finding is significant because rectal bleeding, most often caused by ulcerations of rectal mucosa (2), was the worst symptom in our patients with chronic radiation proctitis. Various therapeutic approaches to these symptoms were proposed: sulfasalazine and oral corticosteroids (17), corticosteroid enemas (7), bipolar electrocoagulation (8), tranexamic acid (18), endoluminal formalin (11,12), and more recently, hyperbaric oxygenation (9), or laser therapy (10). The cases of massive rectal bleeding were significant, and various therapeutic approaches were proposed. However, the use of metronidazole in combination with mesalazine and corticosteroid enemas significantly decreased rectal bleeding and ulcerations, as assessed by rectosigmoidoscopy.
bleeding that could not be managed with conservative methods at ways to acquire sur gi cal therapy (2). We used metronidazole because of its immunomodulation effects (19) and a selective toxicity to anaerobic or microaerophilic microorganisms that can contribute to hypoxia of irradiated rectal tissue (20).

The exact cause of diarrhea during abdominal and pelvic radiotherapy is not known. Although diarrhea usually accompanies rectal mucosal lesion, some authors believe that it is caused by the small intestines in a position in the duodenum. Since the small bowel follow-through contrast study results were normal in our patients, we excluded radiation enteritis as a cause of diarrhea.

Bile acid malabsorption and bacterial contamination by an aerobic and anaerobic bacteria is a common cause of diarrhea after the radiation treatment of gynecological cancer (21). Damage of the pelvic floor and nerves by irradiation may partially explain the experienced urgency of defecation. The physical properties of the rectum, i.e., its compliance and capacity, may also be irreversibly altered (22). Radiotherapy for prostatic cancer also affects the internal anal sphincter causing urgency, increased frequency of defecation, and even incontinence (23,24). In our study, endoanal ultrasound showed that internal anal sphincter was not affected. There are other ways to evaluate anal sphincter functionality, i.e., anal manometry, but for the purpose of this study endoanal ultrasound was sufficient.

Two studies involving patients with chronic radiation proctitis showed that treatment with either sulfasalazine or aspirin was beneficial in improving the symptoms and radiological and proctoscopic signs of proctitis (17,25). Other studies showed that a combination of sulfasalazine with prednisolone (26) and sucralfate in oral form (16) was successful in the treatment of massive diarrhea in radiation proctitis. There was no evidence that the various aminosalicylic acid derivatives and/or corticosteroids given orally or as enema were beneficial in preventing progressive disease (27). Treatment with nonsteroidal anti-inflammatory agents, misoprostol (a prostaglandin E analogue) or sucralfate did not ameliorate or exacerbate radiation proctitis in rats (28).

Danielsson et al (21) also found significant decline in the frequency of radiotherapy in duced diarrhea after treatment with a combination of metronidazole and doxycycline for 7-10 days. In our study, the frequency of diarrhea or the number of defecation episodes, which are probably the most objective parameters, showed a significant downward trend in the metronidazole treatment when compared to the treatment without metronidazole.

Our study also showed that mucosal erythema regressed and mucosal ulcerations healed after metronidazole treatment. Healing of ulcers was also noted by others (29).

Since late radiation proctitis is a result of vascular damage and progressive ischemia of the rectal wall, the usefulness of anti-inflammatory drugs can hardly be expected. So far, most reports could not show local or systemic drug therapy to have any effect on chronic radiation proctitis (6), although there are suggestions that symp toms of radiation in duced proctitis are in most cases reversible and susceptible to conservative treatment (2). Jao and co-workers (2) suggest an aerobic infection as the underlying cause, succeeded in ameliorating rectal pain with metronidazole treatment. In our study, stool cultures were negative for Clostridium difficile, Staphylococcus, Campylobacter, Salmonella, Shigella, ova, or para sites in the stool. Recurrences appeared with similar incidence in both groups, 3 months after the end of the therapy, usually as a reappearance of rectal bleeding and diarrhea.

In conclusion, our study showed that metronidazole in combination with mesalazine and betamethasone enema can be beneficial in the treatment of chronic radiation proctitis and especially in relieving the symptoms such as rectal bleeding and diarrhea. The possible mechanism of metronidazole treatment could be explained by the selective effect on anaerobic and hypoxic cells of rectal mucosa.

References