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Effects of Antibiotics, Anti-Inflammatory Agents, and Monoclonal Antibodies on Liver Function in a TNBS-Induced Crohn's Disease Rat

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Abstract

Background: Crohn's disease is a chronic inflammatory bowel disease characterized by recurring episodes of diarrhea, abdominal pain, and weight loss. Liver involvement is a common extra-intestinal manifestation of Crohn's disease.

Aims: This study aimed to investigate the effects of antibiotics, anti-inflammatory agents, and monoclonal antibodies on liver function in a TNBS-induced Crohn's disease rat model.

Study Design: This was an experimental study using a TNBS-induced Crohn's disease rat model.

Methods: Fifty adult male Sprague-Dawley rats were divided into five groups of ten rats each. The groups included a control group, a Crohn's disease group, and three treatment groups receiving antibiotics (ciprofloxacin), anti-inflammatory agents (prednisolone), and monoclonal antibodies (infliximab), respectively. Serum liver enzymes, total protein, albumin, conjugated bilirubin, total bilirubin, and MDA levels were determined, and liver tissue histological analysis was performed.

Results: The results showed significant increases in liver enzymes (ALP, AST, ALT), oxidative stress markers (MDA), significant decrease in total protein, albumin, conjugated bilirubin, total bilirubin, and histological alterations in the Crohn's disease group compared to the control group. The respective treatment groups showed significant decreases in liver enzymes and MDA levels compared to the Crohn's disease group.

Conclusion: This study demonstrated the

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protective effects of antibiotics, anti-inflammatory agents, and monoclonal antibodies on liver function in a TNBS-induced Crohn's disease rat model. The results suggest that these treatments may reduce liver inflammation and damage by eliminating bacterial translocation, reducing oxidative stress, and inhibiting the production of pro-inflammatory cytokines.

Keywords: Antibiotics, Anti-inflammatory agents, Monoclonal antibodies, Liver, Crohn’s disease

INTRODUCTION

Crohn's disease is a chronic inflammatory bowel disease (IBD) characterized by recurring episodes of diarrhea, abdominal pain, weight loss and fatigue, complications like intestinal stenosis and obstruction, abdominal abscess, fistula, and perianal lesions may occur in some patients due to the progressive nature of the disease. The exact etiology of Crohn's disease remains unclear, but it is believed to result from a complex interplay between genetic predisposition, environmental factors, and an aberrant immune response (1,2). Liver involvement is a common extra-intestinal manifestation of Crohn's disease, with approximately 20-30% of patients developing liver abnormalities, including elevated liver enzymes, cholestasis, and liver failure (3,4).

The management of Crohn's disease typically involves the use of antibiotics, anti-inflammatory agents, and biologic therapies, including monoclonal antibodies (5,6). While these treatments can effectively reduce inflammation and induce clinical remission, their impact on liver function in patients with Crohn's disease is not well understood.

4,6-trinitrobenzene-sulfonic acid (TNBS) is a hapten that induces colitis in rodents, serving as a widely used animal model for studying inflammatory bowel disease (IBD), including Crohn's disease. The TNBS-induced colitis model involves the rectal administration of TNBS, which causes a severe inflammatory response in the colon, characterized by ulcers, inflammation, and diarrhea. TNBS-induced colitis is a widely used animal model of Crohn's disease that recapitulates many of the clinical and pathological features of the human disease, including transmural inflammation, crypt abscesses, and fibrosis (7,8). Using this model, the present study aimed to investigate the effects of antibiotics, anti-inflammatory agents, and monoclonal antibodies on liver function in TNBS-induced Crohn's disease rat model. Specifically, this study examined the impact of these treatments on liver enzyme levels, oxidative stress, and histological changes in the liver. The findings provide new insights into the effects of these treatments on liver function in Crohn's disease and may have important implications for the management of this condition.

MATERIALS AND METHOD

ANIMAL GROUPING

Fifty adult male Sprague-Dawley rats were used for this study and were divided into five groups of ten rats each as showed in the table below.

Table 1. Animal grouping

Group	Treatment
A: normal control	physiological saline (0.9% w/v NaCl, p.o)
B: Crohn's diseases groups	TNBS solution transrectally for six weeks
C: Antibiotics group	TNBS solution transrectally for six weeks and 40 mg/kg of ciprofloxacin (P.O)
D: Anti-inflammatory group	TNBS solution transrectally for six weeks and 100mg/kg of prednisolone
D: MCA B group	TNBS solution transrectally for six weeks and 5 mg/kg of infliximab (i.p)

P.O: oral **i.p: intraperitoneal**

The National Research Council's guidelines for the care and use of laboratory animals were followed in all animal studies and methodology. Ethical approval was obtained from Olabisi Onabanjo University Teaching Hospital Human Research Ethics Committee (OOUTH-HREC), with the number OOUTH/HREC/746/2023AP.

INDUCTION OF CROHN'S DISEASE

The induction of Crohn's disease was done following the method of Morris et al., (9). The Rats were fasted for 24 hours prior to induction of Crohn's disease and was allowed free access to water throughout the study. Crohn's disease was induced by weekly administration of increasing concentrations of TNBS (15, 30, 45, 60, 60 and 60 mg) over 6 weeks. After instillation of TNBS, the rats were then maintained in a head-down position for a few minutes to prevent leakage of the intracolonic instillate.

ADMINISTRATION OF ANTIBIOTICS, ANTI-INFLAMMATORY AGENT AND MONOCLONAL ANTIBODY

Antibiotics, anti-inflammatory agent and monoclonal antibody used in this study were ciprofloxacin Hydrochloride (Ratnamani Healthcare PVT. LTD., India), predilin (Jiangsu Penyao Pharmaceutical Co. Ltd.,China) and infliximab (Cliag AG, Switzerland) respectively. 40 mg/kg of ciprofloxacin was administered every 72 hours for forty-two days orally (10), 100mg/kg of prednisolone was also administered every 72 hours for forty-two days orally (11), and 5 mg/kg of infliximab was administered bi-weekly for forty-two days intra-peritoneal (12).

DETERMINATION OF LIVER FUNCTION TEST

Serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline

Phosphatase (ALP) activities were carried out according to the method of Reitman and Frankel (13). For Serum Alanine Aminotransferase (ALT) determination, diluted sample (0.01mL) was mixed with phosphate buffer (100mM, pH 7.4), L-alanine (200mM) and the mixture was incubated for exactly 30 minutes at 37°C. 0.5 ml of 2, 4 dinitrophenylhydrazine (2mM) was added to the reaction mixture and allowed to stand for exactly 20 minutes at 25°C. Then 5ml of NaOH (0.4 M) was added and the absorbance was read against reagent blank after 5 minutes at 546 nm. Reagent blank was prepared as described above by replacing sample with 0.1 ml of distilled water.

For determination of Aspartate Aminotransferase (AST) activity, 0.1ml of diluted sample was mixed with phosphate buffer (100 mM, pH 7.4), L-asparatate (100 mM), and α-Oxoglutarate (2mM) and the mixture was incubated for exactly 30 minutes at 37°C. 0.5 ml of 2, 4 dinitrophenylhydrazine (2mM) was then added to the reaction mixture and allowed to stand for exactly 20 minutes at 25 0C. Then 0.5ml of NaOH (0.4 M) was added and the absorbance was read against reagent blank after 5 minutes at 546 nm. Reagent blank was prepared as described above replacing sample with 0.1 of distilled water.

Alkaline Phosphatase (ALP) activities was determined using 2.2 ml of 0.1 M carbonate buffer (pH 10.1), 0.1 ml of 0.1 M MgSO4.7H20, and 0.2 ml of the sample were mixed together and incubated at 37 0C for 10 minutes. Thereafter, 0.5 ml of 19 mM of paranitrophenyl phosphate was added and again incubated at 37°C for 10 minutes. 2.0 ml NaOH was added and mixed, and read against blank at 400 nm

Serum protein concentration was determined using the Biuret method (14). Serum albumin levels were measured using the Albumin Diagnostic Kit (citrate buffer pH 4.2, 30 mmol/l, BCG0.26mmol/l), which employs the photometric method described by Jaroslav & Josef (15). This method relies on the ability of bromocresol green (BCG) at pH 4.2 to bind albumin, forming a complex with distinct optical properties.

Using the method described by Tietz (16), serum total bilirubin and conjugated bilirubin was determined based on the principle of bilirubin in the serum that is coupled with diazotized sulphanilic acid to form azobilirubin.

DETERMINATION OF MALONDIALDEHYDE ACTIVITY (LIPID PEROXIDATION)

The MDA activity was measured by the double heating method (17). One ml of tissue homogenate was combined with 2 ml of TCA-TBA-HCL and mixed thoroughly. The solution was heated for 15 minutes in a boiling water bath. After cooling, the flourescent precipitate was removed by centrifugation at 1000g for 10 mins. The absorbance of the sample was determined at 535 nm against a blank that contains all the reagents minus the sample. The malondialdehyde concentration of the sample was calculated using

an extinction coefficeient of 1.56 × 10-5 M-1 Cm-1. Calculation of lipid peroxidation

$$\text{MDA(nmol/ml)} = \boldsymbol{OD} \sum \times \frac{\boldsymbol{V}}{\boldsymbol{v}}$$

OD = Absorbance (optical density) of sample

∑ = Molar extinction coefficient

V = Total volume of the reacting sample

v = Volume of the sample

HISTOLOGICAL ANALYSIS

The organs were carefully removed, and then the fat was removed. After weighing, they were fixed in 10% formal saline right away. The tissues were fixed, placed in progressively higher alcohol grades, and finally cleansed in xylene. After embedding them in paraffin, 5µm serial slices were produced. Hematoxylin and eosin was used to stain the sections. The slides were observed under a light microscope for the histological changes and morphometrical examination.

STATISTICAL ANALYSIS

All the values are expressed as mean ± standard error of mean (SEM). Analysis of data was done using Graph Pad Prism version 5 for Windows. Differences between groups were analyzed by one-way ANOVA followed by Bonferroni post-hoc test. Differences were considered significant at $P < 0.05$.

RESULTS

Table 2 presents the effect of antibiotics, anti-inflammatory agent and monoclonal agent on liver function enzymes and MDA in TNBS induced Crohn's disease rat model.

Table 2. The effect of antibiotics, anti-inflammatory agent and monoclonal agent on liver function enzymes and MDA in TNBS induced Crohn's disease rat model

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)	MDA (µmol/ml)
A	79.33±5.20	39.00±1.52	38.66±3.43	0.20±0.11
B	120.66±4.98[a]	59.00±5.90[a]	65.00±4.80[a]	0.29±0.04[a]
C	95.66±4.84[b]	41.00±0.01	43.33±2.33[b]	0.08±0.05 [ab]
D	63.33±2.16[b]	35.00±2.64[b]	44.66±3.66[b]	0.07±0.04[ab]
E	103.33±2.33[ad]	45.33±3.17	46.33±5.33[b]	0.08±0.04[ab]

Each value is an expression of mean ± SEM. (P <0.05)

a - Values were significant when compared to group A, b-Values were significant when compared to group B, d-Values were significant when compared to group D

Table 3 shows the effect of antibiotics, anti-inflammatory agent and monoclonal agent on total protein, albumin, total bilirubin and conjugated bilirubin in TNBS induced Crohn'sdisease rat model.

Figure 1 indicates the effects on the hepatic tissue through histological examination.

Table 3. The effect of antibiotics, anti-inflammatory agent and monoclonal agent on total protein, albumin, total bilirubin and conjugated bilirubin in TNBS induced Crohn'sdisease rat model

Group	Total Protein	Albumin	Total Bilirubin	Conjugated Bilirubin
A	6.53±0.31	3.60±0.34	0.50±0.15	0.60±0.25
B	3.93±1.42[a]	1.26±0.87[a]	0.16±0.06[a]	0.13±0.03[a]
C	4.46±1.84	3.13±0.43[b]	0.43±0.06[b]	0.33±0.03[b]
D	3.46±1.13[a]	2.60±0.11	0.50±0.01[b]	0.29±0.03[b]
E	4.60±1.96	3.13±1.43[b]	0.53±0.03[b]	0.30±0.05[b]

Each value is an expression of mean ± SEM. (P <0.05)
a - Values were significant when compared to group A, b-Values were significant when compared to group B

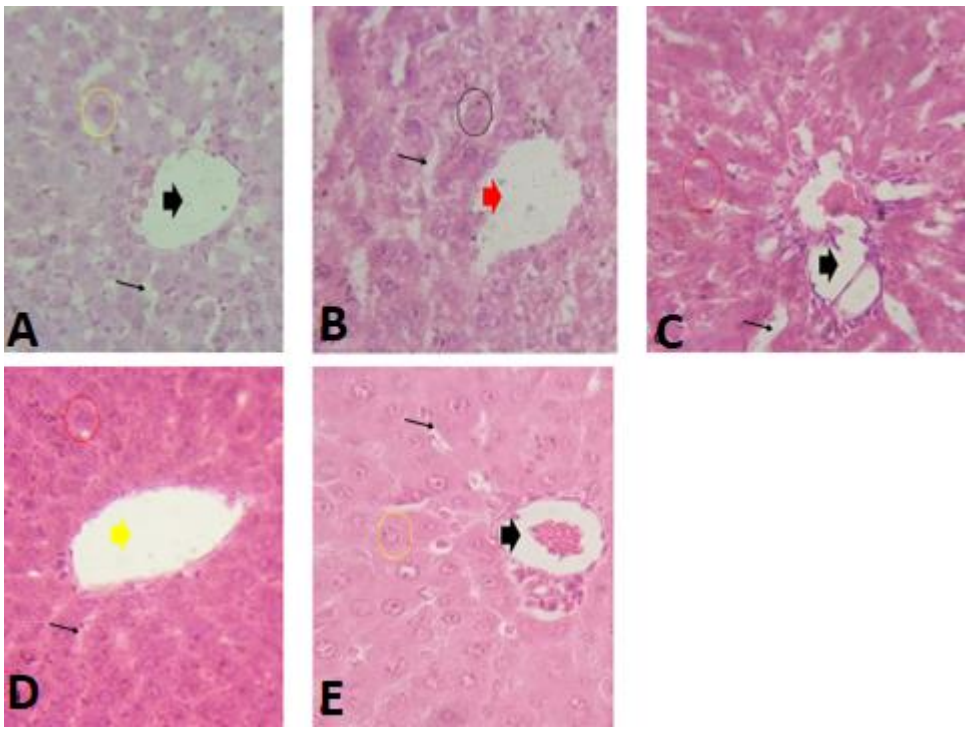

Figure 1. Photomicrograph of hepatic tissue

Group A: showed a well differentiated and organized hepatocytes (yellow circle), sinusoids with kupfer cells (black thin arrow) and clear central vein

Group B: showed a degenerated and distorted hepatocytes (black circle), irregular clear central vein (red thick arrow) and constricted sinusoids (black thin arrow)

Group C: showed a slight distortion of the central vein (black thick arrow), dilated and irregular sinusoids (black thin arrow) with normal hepatocytes (red circle)

Group D: showed a clear central vein (yellow thick arrow), constricted sinusoids (black thin arrow) with slight loss of hepatocytes (red circle)

Group E: showed a slight congestion of the central vein (black thick arrow), hepatocytes (yellow circle) and constricted sinusoids (black thin arrow).

DISCUSSION

This study investigated the effects of antibiotics, anti-inflammatory agents, and monoclonal antibodies on liver function in a TNBS-induced Crohn's disease rat model. The results showed significant increase in liver enzymes, oxidative stress markers, and histological alterations in the Crohn's disease group compared to the control group.

There was a significant increase ($P \leq 0.05$) in AST, ALP, ALT, and MDA levels in the Crohn's disease group indicating liver damage and oxidative stress. Elevated liver enzymes are commonly observed in patients with Crohn's disease, indicating liver involvement in the disease process (18). The elevated MDA levels indicate lipid peroxidation and oxidative stress, which may contribute to liver damage associated with Crohn's disease, including Primary Sclerosing Cholangitis (PSC), Autoimmune Hepatitis, Fatty Liver Disease, Liver Abscesses, and Cholestasis, as reported in previous studies (19-24).

The respective treatment groups showed significant decreases in the liver enzymes and MDA levels compared to the Crohn's disease group, indicating the protective effects of antibiotics, anti-inflammatory agents, and monoclonal antibodies on liver function. The significant decrease in AST levels in the anti-inflammatory group compared to the monoclonal antibody group suggests that anti-inflammatory agents may have a more pronounced effect in reducing liver inflammation (25, 26).

The results also showed a significant decrease in total protein, albumin, conjugated bilirubin, and total bilirubin in the Crohn's disease group indicating impaired liver function and protein synthesis (27, 28). The treatment groups showed significant increases in these parameters, indicating improved liver function and protein synthesis.

Histological examination revealed degenerated and distorted hepatocytes, irregular clear central vein, and constricted sinusoids in the Crohn's disease group, indicating liver damage and inflammation (29). In contrast, the treatment groups showed improved histological features,

with slight distortion of the central vein, dilated and irregular sinusoids, and normal hepatocytes in the antibiotics group.

Antibiotics may reduce liver inflammation and damage by eliminating bacterial translocation and reducing the production of pro-inflammatory cytokines (30), anti-inflammatory agents may reduce liver inflammation and damage by inhibiting the production of pro-inflammatory cytokines and reducing oxidative stress (31,32), and monoclonal antibodies may reduce liver inflammation and damage by targeting specific inflammatory pathways and reducing the production of pro-inflammatory cytokines (33,34).

CONCLUSION

This study demonstrated the protective effects of antibiotics, anti-inflammatory agents, and monoclonal antibodies on liver function in a TNBS-induced Crohn's disease rat model. The results suggest that these treatments may reduce liver inflammation and damage by eliminating bacterial translocation, reducing oxidative stress, and inhibiting the production of pro-inflammatory cytokines.

The major strengths of this study include the use of a well-established TNBS-induced Crohn's disease rat model, which allowed for the investigation of liver function in a controlled and relevant setting. Additionally, the study employed a comprehensive approach, examining the effects of multiple treatments on liver function and inflammation.

However, this study has some limitations. The use of a rat model may not fully translate to human Crohn's disease, and further studies are needed to confirm these findings in clinical settings. Moreover, the study focused on the short-term effects of treatments and did not investigate long-term outcomes or potential side effects.

Despite these limitations, this study provides valuable insights into the potential benefits of antibiotics, anti-inflammatory agents, and monoclonal antibodies in reducing liver inflammation and damage in Crohn's disease. Future studies can build upon these findings to develop more effective therapeutic strategies for managing liver complications in Crohn's disease.

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