

Effects of *E.coli* O157:H7 Experimental Infections on Rabbits

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Received: 01/04/2019

Accepted: 15/07/2019

Publishing: 04/08/2019

Summary

The study aimed to show the effect of experimental infection with *E.coli* O157:H7 on some liver and kidney function in adult rabbits. Twenty five domestic rabbits (males and females), aged 6-8 weeks and weighing 1500-2000g, had a negative fecal bacteriological culture of *E.coli* O157:H7 were used. The rabbits were randomly divided into two groups: infected group (15 rabbits), each animal was drenched orally with 1ml of Phosphate buffer saline containing (2×10^9 CFU) of *E.coli* O157:H7, while the control group (10 rabbits) were drenched orally (1ml) of Phosphate buffer saline, the clinical signs were daily observed for 30 days, recording of body weight and blood samples were collected at (0, 3, 15 and 30) days for serum to evaluate biochemical tests including Alanine transaminase, Aspartate aminotransaminase and alkaline phosphatase, creatinine, urea and total serum protein. The results showed different clinical signs after inoculation, including diarrhea, lethargy, weight loss, inability to eat or drink, urine was cloudy or milky, while control group remains in normal condition. The serum biochemical tests in infected group showed a significant increase of three enzymes at 15, and 30 days, the highest values of Alanine transaminase; Aspartate aminotransaminase and alkaline phosphatase showed at 30 days post infection as compared with the control group. Serum creatinine and urea recorded a significant increase ($P < 0.05$) at 30 day post infection as compared with control group. However, total protein revealed a significant decrease in the infected group, and a significant decrease was noticed at 15 day post infection, while the control group showed an increase in total protein co-ordinated with increase of body weight and progressing age. This study concluded that the infection with *E. coli* O157:H7 may cause changes in liver and kidney functions which were more severe at 15,30 days post infection.

Keywords: *Escherichia coli* O157:H7, serum biochemical testes liver, kidney, rabbit.

Introduction

Escherichia coli O157:H7 is an important zoonotic pathogen (1-3) because of its widespread, peculiar tolerance to some physical and chemical treatments, severity of illness and low dose of infectiveness (4 and 5). This bacterium expresses two virulence factors, the bacterium have ability to produce Shiga toxins (Stx) which encoded by genes present in lambdoid bacteriophages (6 and 7) and the ability to attached intimately to epithelial cells through expressed of the pathogenicity island called locus of the enterocyte effacement (LEE) (8).

E.coli O157 :H7 possess O157 (somatic antigen, O) and 7 Flagellar Antigens (H), this bacterium was recognized firstly as a pathogen of gastrointestinal tract during 2 outbreaks of hemorrhagic colitis in 1982 in Oregon and Michigan (USA), this strain has the capacity to synthesize so called a Shiga

toxin / Vero cytotoxin (9). ELISA test was used for detection of *E. coli* O157 Antigen (10). Although it has been nearly 30 years since the discovery of *E. coli* O157:H7 as an enteric pathogen, no effective treatment exists because the organism is resistant to almost all antibiotics. Moreover, treatment with antibiotics may promote the expression of toxins from the lysogenised phage that carries Shiga-like toxins genes inherent in this organism (11 and 12).

Many enzymes found in hepatocytes can be measured in the serum and are used as assays of liver function (13). Alanine transaminase (ALT) and Aspartate aminotransaminase (AST) are known as transaminase they are associated with the inflammation and liver cells injury, a variety of abnormal conditions will elevate liver enzymes, damage of the liver results in a leak of enzymes AST and ALT into the blood

stream, because of AST was found in other organs, including kidney, muscle, intestine and heart, have high level of AST does not always but indicate there is a problem with liver conversely, high level of serum transaminase could be due to herbal toxicity, liver tumors, fatty liver and heart failure (14 and 15). The greatest activity of ALT in the primates, cats, dogs, rats and rabbits is in liver, it is established, sensitive liver-specific of damage indicator, it is used as an indicator of the hepatopathy in toxicological studies which use small laboratory rodents as well as dogs (16).

ALP enzyme is usually found in the wall of the intra and extra-biliary ducts but it is not specific to the biliary tract, also it is found in bone, intestine and placenta, elevation of ALP may indicate any injury to the biliary cells, common causes of this injury were gall stone in chillsithosis and certain medications. Elevation of this enzymes was found in the late stage of pregnancy, intestinal infection, bone disease, and leukemia, however the ALP is elevated in healthy people especially among older people (17).

Creatinine, is the anhydride of the creatine, is formed in the muscle by non-enzymatic /dehydration of creatine phosphate (18), thus, creatinine remains the most widely used in the laboratory test that estimates the renal function both in an asymptomatic patients and in persons suspected having renal disease to reach maximize its utility, creatinine must be interpreted in light of the clinical information such as weight, age, gender, stability of function of renal, muscle mass, and the degree of catabolism (19).

Proteins are present in the body fluids, but plasma proteins are examined mostly for diagnostic purposes, over 100 individual proteins possess physiological function (humoral immunity, transport, maintenance of oncotic pressure, buffering, enzymes, protease inhibitors,) in plasma, (20 and 21). Changes protein concentration in serum resulting in a variety of systemic effects and clinical signs and are associated with disease processes (22).

Therefore, this study were aimed to evaluate the serum enzymes of liver and kidney functions in rabbits experimentally infected with *E.coli* O157:H7.

Materials and Methods

E.coli O157:H7 were isolated on pediatric hospital from child aged 1 year suffer from diarrhea that, initially, all methods of culturing, Gram stain and Biochemical test were done according to (23). Then culturing on Sorbitol MacConkey agar + cifaxime potassium tellurite and on Chrom agar specifically for *E .coli* O157:H7. Then serotyped was confirmed by using Latex agglutination test for *E.coli* O157 by using the commercial Kit Wellcolex *E.coli* O157:H7, Remel (24).

Infectious dose of *E.coli* O157:H7 were estimated on mice (25). Then the viable count of the bacteria was made by serial dilution plated and incubated for 24 HR/ at 37° C according to the method of (26).

Twenty five rabbits (6-8 weeks age) were randomly divided into two groups as follows: Infected group (No:15): Rabbits were fasted overnight and drenched with 1ml of 10% sterile sodium bicarbonate to neutralize the gastric acidity, after two hours these rabbits drenched orally with 1 ml of the prepared and calculated infectious dose (2X10⁹ CFU) of *E.coli* O157:H7. Control group: (No:10): Rabbits were fasted overnight and drenched with 1ml of 10% sterile sodium bicarbonate orally then drenched with 1m phosphate buffer saline(PBS).

All rabbits were examined clinically about abnormal stools, lethargy, decreased of appetite, body weight, diarrhea and dehydration, also any change in activity, behavior, mortality of the rabbits was recorded throughout the experiment. Blood samples: blood samples were collected at zero time before infection at 3,15 and 30 days after induced infection, Serum was separated from coagulated blood samples by centrifugation at 3000 rpm for 15 minutes and stored at (-20C°) until used for biochemical tests (27). The body weight of rabbits was recorded at 3, 15and 30 days post infection throughout this study.

Biochemical tests- : six Reflotron® test strips were used in this study to determine liver and kidney function test . All strips Serum Alkaline Phosphatase (ALP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Creatinine and Urea

were used in this study and produced from Roche/German Company .

ALP activity (IU/L) was measured by reflotron (28). AST activity (IU/L) and ALT activity (IU/L) activity were measured by reflotron (29). Determination of total protein in serum by Colorimetric method was done by spectrophotometer using (Biolabo/ France) kit. Statistical analysis was conducted to determine the statistical differences among the groups by using ready-made statistical design: statistical package for social science (SPSS).

Results and Discussion

All rabbits in infected group showed a different clinical manifestation post infection with *E.coli* O157:H7. Each rabbit was monitored daily for any clinical manifestation, the important clinical signs was diarrhea, lethargy and loss of body weight compared with the pre-inoculation weight, and absence of movement around the cages when stimulated manually (ear or toe touch or pinch), cloudy urine. After twenty four hours of infection showed a signs, frequent urination, dyspnea, emaciation and diarrhea occurred in 5 out of 15 infected animals after 3 day post infection. This results was agreed with pervious study (30 and 31) who reported urinary tract infection with *E.coli* developed fever, foul smelling , cloudy urine, loss of appetite and unable to rise body occur within less than 24 hours.

The infected group showed an increase of water intake may belong to the increase of temperature with diarrhea, this lead to loss of fluids and dehydration this coincided with (32 and 33). Anorexia occurred with infection suggests that this signs may be a part of the acute response phase, it seems that the food intake should be suppressed voluntarily at time when the metabolic rate can rise to 10-13 % for each C° rise in body temperature, the infection induced anorexia is believed to be a major factor in negative nitrogen balance and the body weight loss that so occurs with

infection (34), this hypothesis examined by injection of endotoxin *E.coli* into rats which results of an increase in body temperature and food intake depression (35).

The results showed changes in the body weight (rabbit/ week) which gave the evidence of correlation between the two groups of rabbits, after infection, A significant decrease ($P<0.05$) in the body weight at 15 and 30 days in infected group as compared with control group (Table, 1)

These results are in agreement with (34), who reported a loss and a decrease in body weight after infection with a pathogenic *E.coli*. The same pattern was noticed at 2nd week in the infected group it's significantly decrease in comparison with the control group .

Our results were compatible with results of (14 and 36) they recorded that the infection induced anorexia that was associated with loss body weight in infected rabbits with *E. coli*. Therefore, body weights loss began as food intake progressively decreases, so infected rabbit's loss more body weight. The highest body weight loss occurred during the period of infection with *E. coli* may be due to the elevated protein breakdown during the acute and chronic septic phases resulting in significant muscle wasting, moreover, sepsis causes a severe and persistent loss of body protein and body weight (37). In other study (38) which attributed the decrease of food intake to *E. coli* lipopolysaccharide endotoxin which induces symptoms of acute bacterial infection including anorexia and fever, also LPS endotoxin resulted in a variety of the morphological change in digestive tract, this may reduce food intake, it was revealed that food intake is correlated with the intestinal change morphology, they found that anorexia during infection may act to reduce the availability of essential nutrients to the growth of pathogens .

Table, 1: Effect of *E.coli* infection on body weight (g) of infected group compared with control group at 3, 15 and 30 days post infection.

| Groups | Body weight post infection/ days (mean ±SE) | | |
|----------------|---|--------------|---------------------|
| | 3days | 15days | 30days |
| Control group | 1500 ± 1.72B | 1800 ± 0.13A | 2000 ± 0.40A |
| Infected group | 1700 ± 0.45A | 1550 ± 2.05B | 1400 ± 0.56B |

*Different letters A and B vertically /refers to the presence of significant differences at (P< 0.05).

Biochemical tests: Rabbits in the infected and control groups showed ALT activity (9.39±0.33, 9.59±0.35) IU/L respectively with no significant difference between them before starting experiment at zero time. The inoculated group with the infectious dose of *E.coli* O157:H7 showed a significant increase (P<0.05) at 3, 15, and 30 days, and the higher value of ALT appeared in the day15 and day 30 (22.84±1.03, 26.30±0.80), as compared with the control group (8.89 ± 0.34) (9.18 ± 0.24) respectively (Table, 2).

Table (3) demonstrated the mean values of AST activity at zero time (9.43±0.17, 10.00±0.45) the values of AST between group remains normal; but in the infected group the results showed a significant increase (P< 0.05) at 3, 15, and 30 day post infection (13.36±0.66, 20.16±1.37, 24.26±1.67) as

compared with the control group which remains within the normal range at different times of the experiment (10.24±1.26, 10.55±0.44, 9.24±0.23).

At zero time, all rabbits showed normal value of ALP. While post-infection showed a significant increase (P<0.05) in ALP after 3, 15, and 30 days (25.38±0.84, 32.34±0.66, 38.44±1.73) in compared to the control group (21.36±0.56, 20.47±0.23, 19.85±0.75) (Table, 4).

The values of creatinine remain normal at the beginning of experiment, but in the infected group, showed a significant increase (1.42± 0.21, 1.20±0.65, 1.21±0.57) (P< 0.05), as compared with the control group range(1.93±0.24, 2.74±1.83, 3.22±0.37) during different times of the experiment (Table, 5).

Table, 2: Effect of *E.coli* infection on ALT(IU/L) value of infected group compared with control group at zero time, 3, 15 and 30 days post infection.

| Time | ALT(IU/L) VALUE (Mean ± SE) | |
|-----------|------------------------------|----------------|
| | Control group | Infected group |
| Zero time | 9.39 ± 0.3 | 9.59 ± 0.35 |
| 3days | 8.91 ± 0.26 B | 12.88 ± 0.46 A |
| 15days | 8.89 ± 0.34 B | 22.84 ± 1.03 A |
| 30days | 9.18 ± 0.24 B | 26.30 ± 0.80 A |

*Different letters A and B horizontally refers to the presence of significant differences

Table, 3: Effect of *E.coli* infection on AST (IU/L) value of infected group compared with group at zero time, 3, 15 and 30 days post infection.

| Time | AST (IU/L) value (Mean ± SE) | |
|-----------|------------------------------|----------------|
| | Control group | Infected group |
| Zero time | 9.43 ± 0.17A | 10.00 ± 0.45A |
| 3 days | 10.24 ± 1.26 B | 13.36 ± 0.66 A |
| 15days | 10.55 ± 0.44 B | 20.16 ± 1.37 A |
| 30 days | 9.42 ± 0.23 B | 24.26 ± 1.67 A |

*Different letters A and B horizontally refers to presence of significant differences at (P< 0.05).

Table, 4: Effect of *E. coli* infection on ALP (IU/L) value of infected group compared with control group at zero time, 3,15 and 30 days post infection.

| Time | ALP (IU/L) value (Mean ± SE) | |
|-----------|------------------------------|----------------|
| | Control group | Infected group |
| Zero time | 20.88 ± 0.29A | 21.22 ± 0.41A |
| 3 days | 21.36 ± 0.56 B | 25.38 ± 0.84 A |
| 15 days | 20.47 ± 0.23 B | 32.34 ± 0.66 A |
| 30 days | 19.85 ± 0.75 B | 38.44 ± 1.73 A |

*Different letters A and B horizontally refers to presence of significant differences at (P< 0.05).

Table, 5: Effect of *E.coli* infection on creatinine value of infected group compared with control group at zero time, 3,15 and 30 days post infection.

| Time | Control group | Infected group |
|-----------|---------------|----------------|
| Zero time | 1.23 ± 0.06A | 1.22 ± 0.45A |
| 3 days | 1.42 ± 0.21 B | 1.93 ± 0.24 B |
| 15days | 1.20 ± 0.65 B | 2.74 ± 1.83 A |
| 30 days | 1.21 ± 0.57 B | 3.22 ± 0.37 A |

*Different letters A and B horizontally refers to presence of significant differences at (P< 0.05).

All rabbits showed normal values (31.17±0.81, 30.71±0.31) of urea before starting experiment at zero time. The infected group showed a significant increase (P< 0.05) of urea value at 15 and 30 days post infection (45.74±1.38, 49.35±0.73) and the higher value of urea appeared in the 30 day (49.35± 0.73), as compared with the control group at 15,30 days (Table, 6). Table, 7 showed a significant decrease of total protein in the infected group, there was little decrease at day 3 post infection (50.7±1.19) and the highest decrease appeared at day 15 (45.1±1.38), while the control group showed increase in total protein according to an increase in body weight and age, (53.0±0.21, 57.2±0.25, 60.7±0.12) at 3, 15, 30 days.

These results are in agreement with (39 and 40) who recorded a significant change in the total protein and albumin levels which could be due to liver damage associated with the bacterial infection.

In the present study, the values of liver enzymes in serum reached the peak at 15 and 30 day post infections compared with the control group, these results may explain that the liver enzymes were released into the blood in any disorder of liver, and it needs long time for return to normal values. The results of the current study were agreed with (41) who found an increased serum creatinine level in infected rabbits with pathogenic *E.coli* and report that

the animal suffering from severe destruction in the kidney tissue. The increase in creatinine and Urea could be due to the effect of the micro-organisms and its toxin on the kidneys, also the results is completely agree with (39 and 42) who reported increased creatinine and urea level in case of renal disease.

The present study was aimed to evaluate the changes in concentrations of total protein in serum during experimental infection with *E.coli* O157:H7 in rabbits. The total serum protein concentrations gradually increased with time in the control group, the total serum protein concentrations became significantly higher at P< 0.05 than initial values on 15 and 30 days. By contrast, in infected group the variations of total serum protein concentration is remained weak during the same period although, total protein concentrations tended to increase at the end of the experiment, but was significantly lowered in comparison to control values. Hypoproteinemia occurred in infected group compared with control group were evident when the diarrhea occurred. The significant change in total protein could be due to kidney damage which could be associated with infection, also our findings concluded that the rabbits are susceptible to *E. coli* O157:H7 infection and suggested as a useful models for investigating Enterohemorrhagic *E.coli* infections of humans as recorded by (14).

Table, 6: Effect of *E.coli* infection on urea value of infected group compared with control group at zero time, 3,15 and 30 days post infection.

| Time | Urea(mmol/L) Mean ± SE | |
|----------------|------------------------|----------------|
| | Control group | Infected group |
| Zero time | 31.17 ± 0.81A | 30.71 ± 0.31 A |
| 3 days | 31.00 ± 0.21 B | 36.54 ± 1.40 A |
| 15 days | 30.7 ± 0.25 B | 45.74 ± 1.38 A |
| 30 days | 32.92 ± 0.12 B | 49.35 ± 0.73 A |

*Different letters A and B horizontally refers to presence of significant differences at (P< 0.05).

Table, 7: Effect of *E.coli* infection on total protein value of infected group compared with control group at zero time, 3,15 and 30 days post infection.

| Time | Total protein (g/dl) (Mean ± SE) | |
|-----------|----------------------------------|----------------------|
| | Control group | Infected group |
| Zero time | 51.1 ± 0.46 A | 52.27 ± 0.82 A |
| 3 days | 53.0 ± 0.21 A | 50.7 ± 1.19 B |
| 15days | 57.2 ± 0.25 A | 45.1 ± 1.38 B |
| 30 days | 60.7 ± 0.12 A | 48,6 ± 1.52 B |

*Different lettersA and B horizontally refers to presence of significant differences at (P< 0.05).

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تأثير الخمج التجريبي لجراثيم الأيشيريشيا القولونية O157:H7 على وظائف الكبد في الأرانب دنيا حاتم فاضل الطائي و عفاف عبدالرحمن يوسف*

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الخلاصة

صممت هذه الدراسة لمعرفة تأثير الاصابة التجريبية للايشيريشيا القولونية O157:H7 على وظيفة الكبد والكلية في الارانب. تم استخدام 25 ارنب (ذكور و اناث) تراوحت اعمارهم بين 6 و 8 اسابيع و باوزان (1500-2000) غم. قسمت الارانب عشوائيا الى مجموعتين: مجموعة الاصابة: وتضمنت 15 ارنب جرعت فمويا ب 1 مل من جرعة الاصابة المحضرة و المحسوبة الحاوية على (2 109 X من جرثومة الايشيريشيا القولونية O157:H7 و مجموعة السيطرة: فقد تضمنت 10 ارناب جرعت فمويا ب 1 مل من محلول الملح الفسيولوجي. ثم لوحظت العلامات السريرية يوميا لمدة 30 يوما بتسجيل وزن الجسم و جمع عينات الدم باوقات مختلفة (0 و 3 و 15 و 30) يوم بعد بدء التجربة و استخدم المصل لتقييم الاختبارات الكيميوحيوية وشملت ALT و AST و ALP والكرياتنين والبروتين الكلي و اليوريا. اظهرت النتائج علامات سريرية مختلفة بعد التجريع، حيث ظهرت علامات الاسهال وارتفاع الحرارة و فقدان الوزن و عدم القدرة على الاكل و الشرب. تغير لون البول الى اللون الحليبي. بينما لم تظهر مجموعة السيطرة اي تغير. اظهرت نتائج التحليل الكيميوحيوي لامصال مجموعة الاصابة بالجرعة الخمجية للأيشيريشيا القولونية زيادة معنوية للانزيمات AST; ALT و ALP في الايام (15 و 30) و اعلى قيمة زيادة كانت في يوم 30 مقارنة بمجموعة السيطرة التي بقيت بالمستوى الطبيعي طوال فترة التجربة. سجل الكرياتنين واليوريا في مجموعة الاصابة زيادة ملحوظة معنويا ($P < 0.05$) في يوم 30 بعد الاصابة مقارنة بمجموعة السيطرة على التوالي. بينما اظهرت نتائج البروتين الكلي نقص معنوي في مجموعة المصابة، بينما لوحظ زيادة في مستوى البروتين الكلي في مجموعة السيطرة مقارنة بزيادة الوزن وتقدم العمر. نستنتج من هذه الدراسة ان الاصابة بجراثيم الايشيريشيا القولونية O157:H7 تسببت بتغيير في وظائف الكبد والكلية والتي ظهرت شدتها في مختلف ايام الاصابة. الكلمات المفتاحية: الايشيريشيا القولونية O157: H7 ، التحليل الكيميوحيوي المصلي للكبد و الكلى ، الأرنب.