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A TRIAL FOR THE TREATMENT OF NEWLY BORN CALVES WITH ENTERITIS BY FLORFENICOL

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ABSTRACT

Neonatal calf diarrhea (NCD) represents a significant economic burden in cattle farms, primarily associated with severe dehydration, metabolic acidosis, and electrolyte imbalances. This study investigated the comparative pharmacodynamic effects of florfenicol myotherapy versus combined florfenicol and oral rehydration powder (ORP) therapy in managing NCD, focusing on hepatorenal function, immune response, and mineral homeostasis in diarrheic calves. This study enrolled a total of 20 native mixed-breed calves, aged 2-3 weeks, and randomly allocated them into four equal groups (n=5 per group). G1 served as a negative control group comprising clinically healthy calves. G2 served as a positive control group consisting of untreated diarrheic calves (fecal score ≥3/5). G3 included diarrheic calves treated with therapeutic doses of florfenicol, while G4 involved diarrheic calves subjected to therapeutic doses of florfenicol and ORP. Bacteriological analysis identified four *E. coli* serotypes (O26, O55, O115, and O146) with prevalence rates of 37.03%, 29.62%, 18.51%, and 14.81%, respectively. Antimicrobial susceptibility testing of isolates against amoxicillin-clavulanic acid, amikacin, ciprofloxacin, erythromycin, gentamycin, ceftriaxone, and florfenicol revealed that florfenicol demonstrated the highest efficacy against the isolated pathogens and was therefore selected for therapeutic intervention**.** Untreated diarrheic calves exhibited significant hepatorenal dysfunction, marked by elevated liver enzymes and altered renal function parameters, alongside disturbed mineral homeostasis. While using florfenicol alone was effective against bacteria, it caused a noticeable increase in liver enzymes (ALT, AST, and ALP) and kidney markers (serum urea and creatinine). Conversely, the combination therapy maintained optimal electrolyte balance and showed only transient elevations in IgM and IgG levels, compared to sustained increases observed in mono-therapy. The florfenicol-ORP combination greatly reduced the negative effects linked to using florfenicol alone, while maintaining immunological and mineral balance. These findings suggest that using a combined treatment approach might be the best way to treat NCD, possibly lowering complications and improving clinical outcomes.

Key words: Florfenicol, ORP, Pharmacodynamic, Diarrhea, Calves

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INTRODUCTION

Among bovine pathological conditions, neonatal calf diarrhea (NCD) stands as the most prevalent disease entity requiring therapeutic intervention in cattle production systems (Eibl *et al.,* 2021). This condition, particularly affecting calves under four weeks of age, represents a paramount health challenge in bovine production, manifesting in substantial economic losses attributed to elevated morbidity and mortality rates (Bhat *et al.,* 2017). NCD is a primary cause of mortality in dairy calves under three weeks of age, accounting for over 75% of deaths in this age cohort (Radostits *et al.,* 2007). The pathogenesis is complex, involving the interplay of environmental factors, pathogenic agents, and inherent calf traits (Foster and Smith, 2009; Randhawa *et al.,* 2012; Cho and Yoon, 2014). Diarrhea in calves may result from infectious agents, including bacteria, viruses, and protozoa, or from nutritional factors that alter intestinal osmotic pressure (Blanchard, 2012). Acute diarrhea in calves is often associated with infectious agents such as enterotoxigenic *E. coli*, *Cryptosporidium parvum*, *Salmonella dublin*, *Salmonella typhimurium*, Rotavirus, and Coronavirus, either singularly or in conjunction (De La Fuente *et al.,* 1998). Notably, E. coli K99+ has been identified as the primary pathogen in calves with scours younger than two months (Acha *et al.,* 2004). Epidemiological studies consistently demonstrate that Enterotoxigenic *E. coli* is a particularly significant cause of diarrhea during the first four days of life in both beef and dairy calves (Myers and Guinee, 1976; Acres *et al.,* 1977; Sherwood *et al.,* 1983; Acres, 1985).

NCD`s pathophysiological consequences are severe, with significant water and electrolyte losses due to damage to the intestinal mucosa, which increases susceptibility to secondary bacterial infections (Miqueo *et al.,* 2018). The resulting metabolic abnormalities, including dehydration, metabolic acidosis, and electrolyte imbalances, vary in severity based on infection intensity and significantly impact calf survival rates (Sen and Constable, 2013; Constable *et al.,* 2017). Notably, mortality primarily results from dehydration and electrolyte depletion, rather than direct pathogenic effects (Smith and Berchtold, 2014).

Treatment strategies prioritize oral rehydration solutions (ORS) with sufficient sodium levels to restore extracellular fluid balance (Miqueo *et al.,* 2018). However, optimal formulation parameters, including pH, osmotic pressure, electrolyte composition, and energy source, remain subjects of ongoing research (Sayers *et al.,* 2016).

The synthetic broad-spectrum antimicrobial agent florfenicol, a chloramphenicol derivative, has emerged as a pivotal therapeutic intervention exclusively designated for veterinary applications (Dowling and Lardé, 2024), demonstrating significant clinical efficacy across various veterinary conditions (Dumka and Singh, 2014). As a member of the amphenicol class, it is widely used in veterinary medicine and aquaculture (Elitok *et al.,* 2015; Shah *et al.,* 2016). In contrast to chloramphenicol and thiamphenicol, florfenicol resists inactivation by acetyltransferase enzymes, maintaining efficacy against resistant strains (Sams, 1994; Kobal, 2004). Its mechanism of action involves binding to the 50S ribosomal subunit (Cannon *et al.,* 1990; Dowling, 2013), inhibiting bacterial protein synthesis, and demonstrating effectiveness against both Gram-positive and Gram-negative bacteria, including chloram-phenicol-resistant strains (Trif *et al.,* 2023).

Florfenicol exhibits significantly lower resistance rates (29%) among *E. coli* isolates from bovine neonatal diarrhea. Recent antimicrobial susceptibility data demonstrate florfenicol's enhanced efficacy compared to conventional antibiotics, which show resistance exceeding 50% (Jia *et al.,* 2022).

This study aimed to investigate the comparative pharmacodynamic effects of florfenicol monotherapy versus a florfenicol-oral rehydration powder combination on hepatorenal biomarkers, serum immunoglobulins, and electrolyte homeostasis, along with bacteriological isolation and virulence gene profiling of diarrhea-causing pathogens in neonatal calves.

MATERIAL AND METHODS:

1. Medications

1.1. Florfenicol (100 mg/mL, Intervet International GmbH, Germany) was administered intramuscularly in the neck region at a dose of 20 mg/kg BW, with a repeated dose after 48 hours (Elitok *et al.,* 2015).

1.2. Oral rehydration powder (Univet Co., Egypt) containing dextrose monohydrate, sodium chloride, sodium citrate, potassium chloride, monopotassium phosphate, calcium pantothenate, and B-complex vitamins (B1, B2, B6) was administered at a dose of 100 g dissolved in 2 L drinking water twice daily for 3 consecutive days.

2. Experimental design and treatment

2.1. Experimental protocol

This study was conducted on a private farm in Kafr El-Ziat, Gharbyia Governorate, and at the Animal Health Research Institute (AHRI), Tanta Lab., and Dokki Lab. chemistry department (chemistry and pharmacology units).

Twenty native mixed-breed calves aged 2-3 weeks and weighing between 25-35 kg were housed in outdoor facilities with concrete-floored pens equipped with weather-protected open-front shelters. Pens were cleaned and disinfected daily. The calves received a non-medicated milk replacer twice daily at body temperature. Calves had *ad libitum* access to both non-medicated calf starter (20% crude protein) and clean drinking water. The experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of the Agriculture Research Center, Egypt (Protocol No. ARC-AHRI/121/24), and all procedures were performed in compliance with institutional guidelines for animal research.

Twenty calves were divided into four equal groups, each containing five animals. The first group (G1) served as a clinically healthy control group and received no treatment. The remaining three groups consisted of diarrheic calves exhibited symptoms including diarrhea, depression, varying degrees of dehydration, inappetence, weakness, dry coat, and, in some cases, retarded growth and recumbence. The *in vitro* antibiotic sensitivity test of rectal swabs was carried out by using the disc method described by Plair *et al.* (1970). The used antimicrobial discs were amoxicillin-clavulanic (AMC, 30 µg), amikacin (Ak, 30 µg), ciprofloxacin (Cip, 5 µg), erythromycin (E, 15 µg), gentamycin (CN, 10 µg), ceftriaxone (CRO, 30 µg), and florfenicol (FFC, 30 µg). The causative agent was more sensitive to florfenicol than other used antimicrobial agents. According to the results of the antibiotic sensitivity testing, the second group (diarrheic calves) served as infected, non-treated control. The third group (diarrheic calves) received therapeutic doses of florfenicol. The fourth group (diarrheic calves) received therapeutic doses of florfenicol along with oral rehydration powder.

The clinical observation was conducted daily; fecal scores were assessed daily, as described by Larson *et al.* (1977), who categorized scores according to feces fluidity as follows: (1) Normal and firm, (2) loose but with general healthy appearance, (3) very loose with no watery separation, (4) watery, and (5) very watery.

2.2. Clinical Examination

Clinical examinations were conducted daily throughout a 10-day experimental period (day 0 to day 10). During each examination, vital parameters were monitored, including rectal temperature, respiratory rate, and heart rate. Fecal consistency scoring was performed daily to assess the progression of diarrhea throughout the observation period.

2.3. Sampling

A. Fecal samples

Fecal samples were collected via rectal swabs on days 0, 4, and 10 of the experiment, with five samples obtained from each group (n=20 per sampling day). Prior to sample collection, the anal area was cleaned. Sterile swabs were carefully inserted into the rectum of each calf and immediately placed in sterile collection containers. All samples were transported to the laboratory under appropriate conditions and processed for bacteriological examination within two hours of collection.

B. Blood samples

Blood samples were collected from the jugular vein of twenty calves (five calves per group) on days 4 and 10 of the experiment using vacutainer tubes (Venoject, Terumo). The samples were allowed to clot at room temperature and centrifuged at 3000 rpm for 20 minutes to separate the serum. Sera were stored at −20°C until analysis. The analysis of biochemical parameters included liver enzymes (AST, ALT, and ALP), protein profile (total protein, albumin, and globulin), kidney function tests (creatinine and urea), pancreatic enzymes (amylase and lipase), minerals (sodium, potassium, phosphorous, calcium, and magnesium), and immunoglobulins (IgM and IgG).

3. Methods

3.1. Bacteriological Examination

A. Isolation and identification

It was carried out according to the technique described formerly by Quinn *et al.* (2002). The collected fecal swabs were inoculated on the same day into the nutrient broth at 37º C for 24 hours, then a loopful of incubated broth was sub-cultured onto nutrient agar, MacConkey's agar, and eosin methylene blue (EMB) media and incubated aerobically at 37º C for 24 hours to check for any microbial growth. The purified bacterial isolates were identified based on their colonial morphology and biochemical characteristics. Smears from pure colonies were prepared and stained using Gram's stain, then examined microscopically for morphological features according to Holt *et al.* (1994).

B.Antimicrobial Susceptibility Testing

Susceptibility tests on Mueller-Hinton agar were performed according to the CLSI (2008) with the guidelines of Schwarz *et al.* (2010).

3.2. PCR procedure:

PCR tests were developed for the specific detection of *Escherichia coli* (*E. coli)* and its virulence genes, which have been made using the following methods:

A.DNA extraction:

DNA extraction from *E. coli* isolates was performed using the QIAamp DNA Mini kit (Qiagen, Germany, GmbH), with modifications from the manufacturer's recommendations.

B.Polymerase chain reaction (PCR) amplification using oligonucleotide primer

The PCR Master Mix and cycling conditions of the primers were prepared according to the EmeraldAmp Max PCR Master Mix (Takara, Japan) kit. The reaction was performed in a T3 Biometra thermal cycler.

Table 1: Primers sequences, target genes, amplicon sizes and cycling conditions:

Target gene	Primers sequences	Amplified segment (bp)	Reference
E. coli phoA	CGATTCTGGAAATGGCAAAAG CGTGATCAGCGGTGACTATGAC	720	Hu *et al.,* 2011
Stx1	ACACTGGATGATCTCAGTGG CTGAATCCCCCTCCATTATG	614	Dipineto *et al.,* 2006
Stx2	CCATGACAACGGACAGCAGTT CCTGTCAACTGAGCAGCACTTTG	779	

Primers used were supplied by Metabion (Germany) and have a specific sequence and amplify a specific product, as shown in Table (1).

3.3. Biochemical analysis

Serum biochemical parameters were analyzed using commercial test kits according to the manufacturers' instructions. All parameters were quantified via spectrophotometric measurements. Liver enzymes were assessed as follows: aspartate transaminase (AST) and alanine transaminase (ALT) according to Reitman and Frankel (1957) and serum alkaline phosphatase (ALP) according to Tietz (1996). Kidney function parameters (urea and creatinine) were determined using kits from Biodiagnostic (Cairo, Egypt), following Newman and Price (1999). The serum protein profile was analyzed using the methods of Henry (1964) for total protein and Doumas *et al.* (1971) for albumin. Pancreatic enzymes were assessed as follows: amylase and lipase according to Badenoch and Bals (1989) and Rietz and Guilbault (1975), respectively. Electrolyte` levels were determined according to the following methods: calcium (Kessler and Wolfman, 1964), phosphorus (Daly and Ertingshausen, 1972), potassium (Sunderman and Sunderman, 1958), sodium (Trinder, 1969), and magnesium (Burtis and Ashwood, 1999). Serum IgM and IgG levels were measured using ELISA kits (Langton, Shanghai, China), following the procedure of Killingsworth and Savory (1972).

4. Statistical Analysis:

The statistical analysis was conducted as follows: The Shapiro-Wilk test was employed to verify the normal distribution of data and homogeneity of variances for biochemical parameters across treatments ($P > 0.05$). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by Duncan's Multiple Range Test for post-hoc analysis. Differences were considered statistically significant at $p \leq 0.05$. All analyses were executed using SPSS software (version 24, IBM Corp., Armonk, NY, USA) (SAS, 2016). Results are presented as mean ± standard error (SE).

RESULTS

1. Bacterial cultures and identification

Morphological examination showed that the suspected colonies were rounded, non-pigmented colonies on nutrient agar medium, while on MacConkey's agar medium, they showed rounded, bright pink colonies (lactose fermenter colonies), and on EMB they showed distinctive greenish metallic sheen colonies, which agreed with the description of *E. coli*. These colonies appeared under the microscope as Gram-negative, motile bacilli microorganisms.

Biochemical identification proved that the isolated strains showed indole production, methyl red test, catalase test, and nitrate reduction test were all positive, while Vogues-Proskauer test, citrate utilization test, triple sugar iron test, oxidase test and urease test were all negative, so the primary identification was *E. coli*. Biochemical and serological examination revealed isolation of *E. coli*, with a total prevalence rate reaching 100% in group 2 (infected but not treated). After treatment with florfenicol, the prevalence was reduced to 40% by the 4th day of the treatment, and complete recovery occurred on the 8th day. While in group 4, which was treated with both florfenicol and oral rehydration powder, showed complete recovery by the 4th day of the treatment (Table 2). *E. coli* isolates were confirmed using PCR via amplification of a genus-specific primer (Figure 1). Serological identification revealed recovery of four *E. coli* serotypes, namely *E. coli* O26, O55, O115, and O146 at 37.03%, 29.62%, 18.51%, and 14.81%, respectively (Figure 2). The recovered *E. coli* isolates harbored *stx1* and *stx2* virulence-associated genes (Figure 3).

Table 2: Prevalence rate of *E. coli* in the examined animals during 8 days of treatment

	GP1	GP 2	GP 3	GP 4
0 day	0	5 (100%)	5 (100%)	5 (100%)
4th day	0	5 (100%)	2 (40%)	0
8th day	0	5 (100%)	0	0

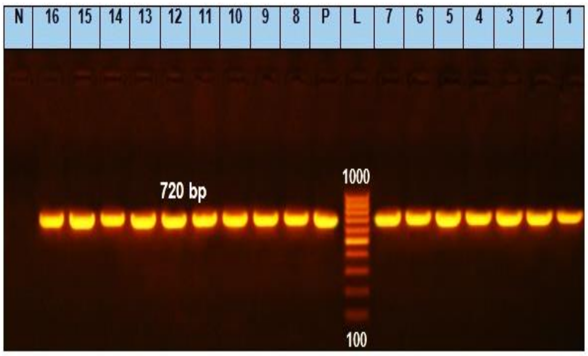

Figure 1: A representative agarose gel electrophoresis for the amplification of phoA gene (720 bp)

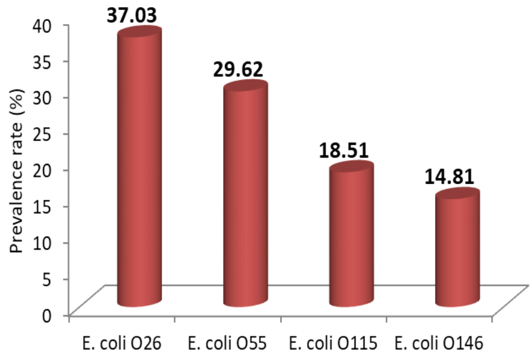

Figure 2: Prevalence rate of different E. coli serotypes recovered in the present study

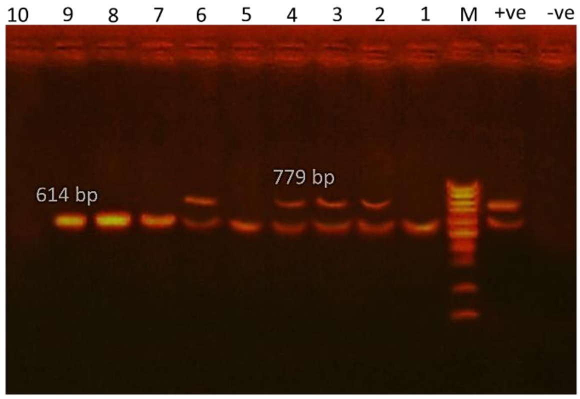

Figure 3: A representative agarose gel electrophoresis for the amplification of stx1 gene (614 bp), and stx2 (779 bp), M (marker), +ve (control positive), -ve (control negative)

The *in vitro* sensitivity tests for ten isolates of *E. coli* revealed that the isolated *E. coli* was highly resistant to amoxicillin-clavulanic (100 %), followed by ceftriaxone and erythromycin (80 % for each), amikacin (70 %), ciprofloxacin (60 %), and gentamycin (50 %). The isolates of *E. coli* were highly sensitive to florfenicol (100 %) (Figure 4).

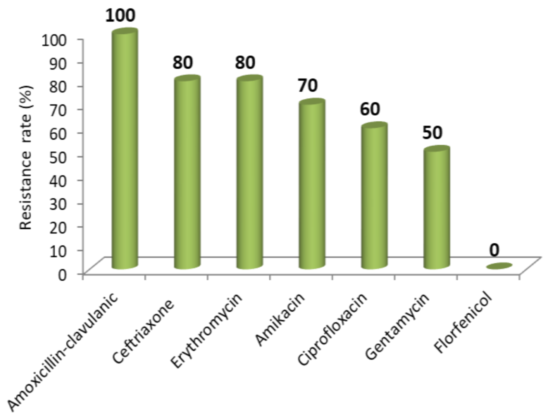

Figure 4: Antimicrobial resistance rates of the recovered *E. coli* isolates in the current study

2. Biochemical Analysis

Table 3: Serum biochemical parameters (mean ± SE) of diarrheic calves treated with florfenicol alone and florfenicol with oral rehydration powder.

Parameter	Group	4th D post-treatment	10th D post-treatment
Alanine transaminase (IU/ml)	GP 1	22.00±1.41 [c]	23.80±0.80[c]
	GP 2	34.40±1.36[a]	42.80±1.06[a]
	GP 3	34.00±1.87 [a]	36.20±1.65[b]
	GP 4	29.85±0.54 [b]	25.80±1.01[c]
Aspartate transaminase (IU/ml)	GP 1	36.80±2.32 [c]	39.40±1.88[d]
	GP 2	68.60±1.93[a]	78.00±1.51[a]
	GP 3	62.00±2.66 [b]	60.40±3.17 [b]
	GP 4	58.40±0.92[b]	46.00±1.30 [c]
Alkaline phosphatase (IU/ml)	GP 1	56.20±2.15[d]	57.40±2.11[c]
	GP 2	95.60±1.80[a]	101.60±0.74[a]
	GP 3	83.20±1.65[b]	74.40±2.33[b]
	GP 4	69.20±1.39[c]	62.60±1.60[c]
Creatinine (mg/dL)	GP 1	0.97±0.06[c]	1.12±0.03[c]
	GP 2	1.20±0.03[b]	1.30±0.03[b]
	GP 3	1.40±0.05[a]	1.52±0.03[a]
	GP 4	1.20±0.03[a]	1.06±0.02[c]
Urea (mg/dL)	GP 1	28.60±2.63[c]	31.80 ±2.10[c]
	GP 2	45.80±1.11[a]	51.00±1.48[a]
	GP 3	40.60±0.60[b]	37.20±0.73[b]
	GP 4	33.20±1.31[c]	30.00±0.89[c]
Total Protein (g/dl)	GP 1	6.38±0.24[b]	6.92±0.15[b]
	GP 2	7.48±0.21[a]	8.50±0.18[a]
	GP 3	7.44±0.06[a]	6.80±0.09[b]
	GP 4	7.12±0.09[a]	6.84±0.12[b]
Albumin (g/dl)	GP 1	3.32±0.09[a]	3.36±0.09[a]
	GP 2	2.78±0.10[c]	2.54±0.07[b]
	GP 3	3.06±0.04[b]	3.30±0.05[a]
	GP 4	3.28±0.03[ab]	3.44±0.04[a]
Globulin (g/dl)	GP 1	3.06±0.32[c]	3.56±0.19[b]
	GP 2	4.70±0.15[a]	5.96±0.17[a]
	GP 3	4.38±0.05[ab]	3.50±0.13[b]
	GP 4	3.84±0.09[b]	3.40±0.14[b]

Results are represented as mean ± standard error.
The means within the same column carrying different letters are significantly different at P ≤ 0.05
GP 1: Control, GP 2: Infected non-treated, GP 3: Infected treated with florfenicol, GP 4: Infected treated with florfenicol and oral rehydration powder.

Table 4: Serum amylase and lipase (mean ± SE) of diarrheic calves treated with florfenicol alone and florfenicol with oral rehydration powder.

Parameter	Group	4 Days post-treatment	10 Days post-treatment
Amylase (IU/ml)	GP 1	234.00±7.48[d]	313.00±4.89[c]
	GP 2	560.00±21.21[a]	735.00±18.70[a]
	GP 3	418.00±16.24[b]	398.00±6.63[b]
	GP 4	361.40±18.13[c]	300.00±10.00[c]
Lipase (IU/ml)	GP 1	195±4.47[c]	207±3.00[b]
	GP 2	333±5.83[a]	432±8.00[a]
	GP 3	235±11.61[b]	209±4.00[b]
	GP 4	214±2.91[bc]	203±2.00[b]

Results are represented as mean ± standard error.
The means within the same column carrying different letters are significantly different at P ≤ 0.05
GP 1: Control, GP 2: Infected non-treated, GP 3: Infected treated with Florfenicol, GP 4: Infected treated with Florfenicol and oral rehydration solution.

Table 5: Serum biochemical parameters and electrolytes (mean ± SE) of diarrheic calves treated with florfenicol alone and florfenicol with oral rehydration powder.

Parameter	Group	4 Days post-treatment	10 Days post-treatment
Sodium (mmol/L)	GP 1	135.00±0.70[a]	139.20±0.37[a]
	GP 2	130.40±0.92[b]	125.60±0.40[c]
	GP 3	131.60±0.67[b]	133.40±0.50[b]
	GP 4	137.20±0.96[a]	138.00±0.70[a]
Potassium (mmol/L)	GP 1	3.78±0.08[a]	4.04±0.05[a]
	GP 2	3.04±0.05[c]	2.74±0.06[c]
	GP 3	3.18±0.06[c]	3.44±0.06[b]
	GP 4	3.58±0.03[b]	4.02±0.04[a]
Calcium (mmol/L)	GP 1	9.64±0.25[a]	9.90±0.23[a]
	GP 2	8.24±0.10[b]	7.60±0.07[c]
	GP 3	8.60±0.12[b]	8.70±0.12[b]
	GP 4	9.26±0.08[a]	9.96±0.07[a]
Phosphorus (mmol/L)	GP 1	4.56±0.10[a]	4.74±0.10[a]
	GP 2	4.02±0.04[b]	3.20±0.08[c]
	GP 3	4.18±0.05[b]	4.40±0.05[b]
	GP 4	4.44±0.04[a]	4.82±0.03[a]
Magnesium (mmol/L)	GP 1	2.14±0.06[a]	2.30±0.09[a]
	GP 2	1.72±0.03[b]	1.46±0.04[c]
	GP 3	2.00±0.03[a]	2.10±0.03[b]
	GP 4	2.10±0.03[a]	2.20±0.03[ab]

Results are represented as mean ± standard error.
The means within the same column carrying different letters are significantly different at $P \leq 0.05$
GP 1: Control, GP 2: Infected non-treated, GP 3: Infected treated with Florfenicol, GP 4: Infected treated with Florfenicol and oral rehydration solution.

Table 6: Serum IgM and IgG (mean ± SE) of diarrheic calves treated with florfenicol alone and florfenicol with oral rehydration powder.

Parameter	Group	4 Days post-treatment	10 Days post-treatment
IgM (mg/dl)	GP 1	8.34±0.09[d]	9.04±0.09[c]
	GP 2	48.10±0.42[a]	59.52±0.60[a]
	GP 3	16.48±0.24[b]	11.70±0.13[b]
	GP 4	11.74±0.18[c]	9.72±0.12[c]
IgG (mg/dl)	GP 1	30.22±0.49[d]	34.20±0.37[c]
	GP 2	294±2.46[a]	389.00±3.67[a]
	GP 3	93.16±0.29[b]	75.60±0.50[b]
	GP 4	50.60±0.63[c]	34.20±0.26[c]

Results are represented as mean ± standard error.
The means within the same column carrying different letters are significantly different at $P \leq 0.05$
GP 1: Control, GP 2: Infected none treated, GP 3: Infected treated with Florfenicol, GP 4: Infected treated with Florfenicol and oral rehydration solution.

DISCUSSION

Environmental factors interact in multiple ways to induce calf diarrhea infections. The constraints for raising young cattle mostly arise from viral illnesses and the calf itself. Calf diarrhea, a common infection in calves up to three months old, is a multifaceted sickness that poses considerable financial and animal welfare issues in dairy and beef cow populations. The predominant and commercially important bacterial agent of diarrhea in neonatal livestock is E. coli. The current study identified *E. coli* in calves with diarrhea across all experimental groups. Serological identification indicated the recovery of four *E. coli* serotypes: *E. coli* O26, O55, O115, and O146, with relative prevalence rates of 37.03%, 29.62%, 18.51%, and 14.81%. The recovered isolates contained *stx1* and *stx2* virulence genes linked to the start of diarrhea. *E. coli* isolates exhibited significant antibiotic resistance while demonstrating notable sensitivity to florfenicol, which was intended as a therapeutic strategy in this work. Consistent with the results of our investigation, *E. coli* was identified as the primary cause of calf diarrhea globally (Cho and Yoon, 2014; Muktar *et al.,* 2015). *E. coli* was detected in 46.4% of neonatal calf diarrhea episodes in Egypt. Serogroups O1, O26, O44, O55, O115, O119, O125, O146, and O151 were identified in the fecal samples collected, exhibiting the expression of *stx1* and *stx2* genes in the isolated strains. Additionally, the isolated strains showed complete resistance to ampicillin and cefotaxime (100% each), but were sensitive to norfloxacin (80%) (Mohammed *et al.,* 2019).

Untreated infected calves (G2) showed a marked elevation in the activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) enzymes over the study period, compared to the normal control group. The increased enzyme activity signifies compromised liver function in neonatal calf diarrhea. These results align with earlier research conducted by Grodzki *et al.* (1991) and Bozukluhan et al. (2017). Calves administered florfenicol alone (G3) exhibited a notable elevation in ALT, AST, and ALP enzyme activity throughout the experimental periods, compared to the normal control group. This pattern aligns with studies in trout (Er and Dik, 2014; Shiry *et al.,* 2019) and is corroborated by results in goats (Shah *et al.,* 2016; Hamed *et al.,* 2020), consistent with conclusions in rats (Ma *et al.,* 2022), and in line with findings in rabbits (Cazanga *et al.,* 2023). The group administered florfenicol and oral rehydration powder (G4) demonstrated temporary substantial elevations in ALT and ALP enzyme activities, alongside a persistent increase in AST enzyme activity, relative to the normal control group. These enzymes increase is attributed to florfenicol's pharmacokinetics, particularly its distribution in tissues including the liver, lung, heart, and muscles (Adams *et al.,* 1987; Lobell *et al.,* 1994), leading to minor cellular damage (Zilva and Mayne, 1991) and release of these enzymes into the bloodstream (Amacher, 1998). Additionally, florfenicol may induce biliary obstruction or cholestasis, further increasing ALP synthesis in hepatic cells and hence increasing serum concentrations (Center, 2007).

G2 demonstrated significant elevations in urea and creatinine levels over the trial period compared to the normal control group, indicating impaired renal function. These results are consistent with previous studies (Walker *et al.,* 1998; Seifi *et al.,* 2006; Dratwa-Chalupnik *et al.,* 2012). A notable rise was found in G3, but no significant alteration in urea levels occurred in G4 compared with G1 throughout the whole experimental period. This conclusion is corroborated by research conducted by Mckellar and Varma (1996), Shah *et al.* (2016), Miqueo *et al.* (2018), and Hamed *et al.* (2020). A marked elevation in blood creatinine levels was recorded in G3, but a temporary substantial rise was found in G4, compared to G1. Florfenicol's impact on renal function is likely due to its pharmacokinetics, where it diminishes protein levels by inducing protein catabolism and disrupting urea excretion (glomerular filtration), leading to increased blood urea and creatinine concentrations (Salomon *et al.,* 2003; Brophy *et al.,* 2010), while simultaneously affecting creatinine levels due to its predominant renal excretion rate of 64% (Varma et al., 1986; Sams, 1994) and its peak concentrations in kidney tissues (Adams *et al.,* 1987). These findings align with Shah *et al.* (2016), who reported that therapeutic doses of florfenicol have demonstrated reversible short-term harmful effects on kidney and liver function indices in piglets.

Our investigation of serum protein profiles revealed that G2 demonstrated a significant increase in total protein levels, compared to G1. Conversely, serum albumin levels were significantly decreased in G2 relative to G1. Notably, globulin levels were significantly elevated (P<0.05) in G2 throughout the experimental period compared with G1. These findings align with previous observations reported by Seifi *et al.* (2006) and Dratwa-Chalupnik *et al.* (2012). Both G3 and G4 showed a temporary increase in total protein levels and a transient decrease in albumin levels compared with G1. Notably, G3 and G4 demonstrated time-dependent ameliorative effects, ultimately reducing globulin levels to near-control values by day 10. These results support findings by Ghanem *et al.* (2015), Miqueo *et al.* (2018), and Hamed *et al.* (2020), indicating that florfenicol treatment influences blood protein dynamics, causing temporary changes in total protein, albumin, and globulin levels. The concentration of serum globulins consists of numerous proteins produced in the liver, including acute-phase proteins that serve as reactants to tissue injury, resulting in a swift and significant rise in total globulin concentration (Brito Galvao and Center, 2012). This process may explain the substantial rise in globulin and, consequently, total protein noted in the present investigation.

Infected, untreated calves exhibited significantly elevated serum amylase and lipase activities throughout the trial, indicating potential pancreatitis, a condition commonly associated with enterocolitis caused by entero-invasive microorganisms (Reimund *et al.,* 2005). Calves that received only florfenicol demonstrated a persistent increase in serum amylase activity, while those treated with both florfenicol and oral rehydration powder (ORP) showed a temporary, notable elevation in amylase activity compared to the normal control group. Additionally, serum lipase activity was temporarily elevated in the florfenicol-only group, while the florfenicol-ORP group exhibited a transient, non-significant increase in lipase activity. These findings suggest that florfenicol, whether used alone or with ORP, can temporarily change the activity of amylase and lipase enzymes, which might indicate problems with the pancreas during treatment.

Infected, non-treated calves consistently displayed a significant reduction in serum levels of sodium, potassium, calcium, phosphorus, and magnesium throughout the trial duration compared to G1. These results agreed with the previous studies of Groutides and Michell (1990), Walker *et al.* (1998), Smith (2009), Dratwa-Chalupnik *et al.* (2012), Constable and Grünberg (2013), Trefz *et al.* (2013), Tajik and Nazifi (2013), Trefz et al. (2015), Constable *et al.* (2017) and Lee *et al.* (2020).

Furthermore, G3 revealed a significant reduction in serum levels of sodium, potassium, calcium, phosphorus, and magnesium compared with G1 throughout the experiment, which is consistent with Ghanem *et al.* (2015). In contrast, calves treated with both florfenicol and oral rehydration powder (ORP) showed no significant changes in serum levels of sodium, calcium, phosphorus, and magnesium. However, a temporary reduction in serum potassium levels was observed, which matches the findings of Wilms *et al.* (2020) and Wilms *et al.* (2023)

The pathophysiology of diarrhea in calves involves increased secretion and decreased absorption, leading to fluid accumulation and electrolyte imbalances such as hyponatremia and hypokalemia (Dratwa-Chalupnik *et al.,* 2012). Electrolyte disturbances are aggravated by fluid losses through feces, reduced milk intake, and hemoconcentration (Grove-White and Michell, 2001). These findings underscore the complex interplay between fluid balance, electrolyte equilibrium, and acid-base status in diarrheic calves, highlighting the need for effective management strategies to improve clinical outcomes.

Infected, untreated calves exhibited a significant increase in serum IgM and IgG levels throughout the study period, compared to the normal control group. Similarly, calves treated with florfenicol alone demonstrated elevated serum IgM and IgG levels all over the experimental period, supporting the findings of Ghanem *et al.* (2015). Calves that received florfenicol and oral rehydration powder (ORP) showed a temporary substantial elevation in IgM and IgG levels compared with the normal control group. These results highlight the immunological impact of both infection and florfenicol treatment on serum immunoglobulin levels, reflecting the complex interaction between antimicrobial therapy and the immune response. The observed increase is likely due to the inflammatory response induced by the infection, leading to hypergamma-globulinemia, as previously described by Apaydin and Dede (2010).

CONCLUSION

The present study demonstrated that *E. coli* is a significant causative agent of calf diarrhea, with four predominant serotypes (O26, O55, O115, and O146) identified, carrying *stx1* and *stx2* virulence genes. While florfenicol demonstrated antimicrobial efficacy against *E. coli*, its administration induced significant alterations in hepatic biomarkers (ALT, AST, and ALP) and renal parameters (urea and creatinine). Notably, the concurrent administration of oral rehydration powder (ORP) with florfenicol showed a promising therapeutic approach for mitigating these adverse effects. ORP supplementation demonstrated particular efficacy in maintaining electrolyte balance, reducing biochemical alterations, and supporting better therapeutic outcomes compared with florfenicol treatment alone. Additionally, both infection and florfenicol treatment influenced immunoglobulin levels, particularly IgM and IgG, highlighting the complex interaction between antimicrobial therapy and immune response. Based on these findings, we recommend incorporating ORP alongside florfenicol treatment in managing calf diarrhea with regular biochemical monitoring, while implementing preventive measures against *E. coli* infection, and conducting further research to optimize the ORP formulation and treatment protocol for enhanced therapeutic outcomes.

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محاولة لعلاج عجول حديثة الولادة مصابة بالتهاب الأمعاء باستخدام الفلورفينيكول

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يمثل إسهال العجول حديثي الولادة عبئاً اقتصادياً كبيراً في مزارع الأبقار، حيث يرتبط بشكل رئيسي بالجفاف الشديد، الحماض الأيضي واضطراب توازن الإلكتروليتات. هدفت هذه الدراسة إلى تقييم الديناميكية الدوائية للعلاج الأحادي بالفلورفينيكول مقارنة بالعلاج المشترك بين الفلورفينيكول ومسحوق الإماهة الفموية في علاج إسهال العجول حديثي الولادة، مع التركيز بشكل خاص على وظائف الكبد والكلى، والاستجابة المناعية، وتوازن الإلكتروليتات في العجول المصابة. تم إدراج عشرين عجلاً من السلالات المحلية المختلطة بعمر ٢-٣ أسابيع في هذه الدراسة وتوزيعها عشوائياً إلى أربع مجموعات متساوية (خمسة عجول لكل مجموعة). مثلت المجموعة الأولى مجموعة الضبط السلبية التي تضم عجولاً سليمة سريرياً، بينما مثلت المجموعة الثانية مجموعة الضبط الإيجابية المكونة من عجول مصابة بالإسهال غير معالجة (درجة البراز ≥3/5). شملت المجموعة الثالثة عجولاً مصابة بالإسهال عولجت بجرعات علاجية من الفلورفينيكول، في حين ضمت المجموعة الرابعة عجولاً مصابة خضعت للعلاج بجرعات علاجية من الفلورفينيكول ومسحوق الإماهة الفموية.

حدد التحليل البكتريولوجي أربعة أنماط مصلية للإشريكية القولونية (O146, O115, O55, O26) بمعدلات انتشار بلغت 37.03% و29.62% و18.51% و14.81% على التوالي. أظهرت العجول المصابة غير المعالجة خللاً وظيفياً كبدياً كلوياً ملحوظاً تميز بارتفاع إنزيمات الكبد، وتغير معايير وظائف الكلى، إلى جانب اضطراب توازن المعادن. وفي حين أظهر العلاج الأحادي بالفلورفينيكول فعالية مضادة للميكروبات، إلا أنه تسبب في ارتفاعات معنوية في إنزيمات الكبد (ALT, AST, and ALP)والمؤشرات الحيوية الكلوية (اليوريا والكرياتينين في المصل). في المقابل، حافظ العلاج المشترك على التوازن الأمثل للشوارد وأظهر ارتفاعات عابرة فقط في مستويات IgM وIgG، مقارنة بالزيادات المستمرة التي لوحظت في العلاج الأحادي. خفف مزيج الفلورفينيكول ومسحوق الإماهة الفموية بشكل كبير من الآثار الجانبية المرتبطة بالعلاج الأحادي بالفلورفينيكول مع الحفاظ على التوازن المناعي والمعدني. تستخلص هذه النتائج أن النهج العلاجي المتكامل قد يمثل استراتيجية علاجية مثلى لإسهال العجول حديثي الولادة، مما قد يقلل من المضاعفات الفيسيولوجية المرضية ويحسن النتائج السريرية.