Original Article

Allopurinol and Albendazole efficacy against trichinosis in experimentally-infected mice

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ABSTRACT

Background: In trichinosis, current treatments (Albendazole), have limited efficiency in eliminating encapsulated larvae because of poor absorption and potential side effects at higher doses.
Objective: The therapeutic efficacy of allopurinol, given alone or in combination with albendazole, was investigated in a murine model of trichinosis.
Material and Methods: Eighty male albino mice were assigned to two experimental phases: an intestinal phase-experiment I and a muscle phase-experiment II. In each experiment, mice were divided into four treatment groups: infected untreated administered normal saline; treated with albendazole (50 mg/kg); allopurinol (30 mg/kg); and combined treatment. In both experiments, efficacy was evaluated on the 6th, and 45th day of infection, respectively. Parameters used were parasite burden in the intestine and in 3 muscle tissues (tongue, diaphragm, and thoracic muscle), and histopathological examinations.
Results: Albendazole alone reduced intestinal worm burden by 98.53% with limited effect on muscle larvae (56.86-59.44% reduction). Allopurinol showed moderate effect on intestinal worms (69.41% reduction) but with higher efficacy against muscle larvae (83.93-87.36% reduction). The combined therapy was the most effective, reducing intestinal worms by 98.76%, and muscle larvae by 93.69-94.71%. Histopathological examination showed that the combined treatment minimized inflammation and myodestruction with extensive larval degeneration.
Conclusion: Allopurinol showed higher efficiency against muscular trichinosis, while albendazole was more effective against intestinal trichinosis. The combination therapy yielded promising results against both phases, suggesting potential as an improved treatment for trichinosis. Further clinical investigations are recommended to confirm these findings.

Keywords: Albendazole; allopurinol; combined therapy; encysted larvae; intestinal phase; nurse cells; trichinosis.

Received: 26 September, 2024; **Accepted:** 13 December, 2024.

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Print ISSN: 1687-7942, **Online ISSN:** 2090-2646, **Vol. 17, No. 3, December, 2024.**

INTRODUCTION

Trichinosis is an important zoonotic disease, infecting a great number of hosts and distributed worldwide. It is due to nematodes of the genus *Trichinella*[1,2]. Humans get infected by ingesting raw or undercooked pork meat, or adulterated cattle or sheep meat infected with *Trichinella* larvae. Following ingestion, larvae are released in the small intestine where they develop into adult worms. They produce newborn larvae, which then penetrate the intestinal wall and migrate through the bloodstream to skeletal muscles[3,4]. Fever, diarrhea, orbital edema, muscle soreness, weakness, and exhaustion are some symptoms of this migration. The causing species, *T. spiralis*, has a special predilection for skeletal muscle cells in which it forms larval nurse cells[5]. While the enveloped muscle larvae in striated muscle fibers survive for months to years, adults in the colon live for about four to six weeks[6].

The chemotherapy of human trichinosis is mainly based on benzimidazole derivatives such as albendazole, mebendazole, flubendazole, and thiabendazole. However, they are inadequate in eliminating encapsulated and newborn larvae due to low absorption and possible side effects at high doses[7]. Besides, they should not be prescribed for pregnant women, and infants under the age of two years[8]. Therefore, it becomes necessary to discover more effective therapies and new pharmaceuticals. Allopurinol is a well-known drug in the treatment of gout and kidney stones by inhibiting uric acid synthesis[9], and has also been shown to inhibit the growth of intracellular protozoa such as *T. cruzi*[10] and *L. infantum*[11]. Since *T. spiralis* belongs to the category of intracellular parasites residing in the mucosa and muscle cells of the small intestine, at least in theory, it can be susceptible to allopurinol.

The present study was designed to assess the therapeutic efficacy of allopurinol, both as a monotherapy and in combination with albendazole, against experimental murine trichinosis. An animal model of disease was utilized to investigate the effect of allopurinol on the course of infection.

 DOI: 10.21608/puj.2024.324103.1270

MATERIAL AND METHODS

This experimental case-control study was conducted at the Parasitology Department of Theodor Bilharz Research Institute (TBRI) from January 2019 to December 2019.

Study design: A total of 80 male albino mice were divided into two equal experimental groups of 40 mice each. Experiment I focused on the intestinal phase, while experiment II examined the muscular phase. Parameters used for efficacy evaluation included assessment of worm and larval burdens, and histopathological examination of three muscle tissues.

Experimental animals: The experiment was carried out on 80 male albino mice, 6-8 w weighing 25-30 gm. Breeding mice were supplied by European Country Farms in Egypt and housed at TBRI. They were fed a regular diet and kept in the biological unit of TBRI under controlled conditions (24°C). Stool samples were examined to rule out additional parasitic infections.

Mice infection: The *T. spiralis* larvae were isolated from infected mice received from the Parasitology Department, TBRI, and the inoculum preparation and infection induction was conducted as previously described[12]. Mice were orally infected with 200 *T. spiralis* larvae by an insulin syringe connected with an 18-gauge blunt needle[13].

Treatment preparations: Albendazole (Zentel, GlaxoSmithKline) was administered at a dose of 50 mg/kg[14], and Allopurinol (Zyloprim, Prometheus Laboratories Inc.) was used at a dose of 30 mg/kg[15]. Both medications were made from tablets, crushed into a powder, dissolved in distilled water, and administered to the mice *via* an esophageal tube. Treatment started on the second day after infection in experiment I and on the 30th day after infection in experiment II[16].

Study groups: Each experiment was further divided into four groups of ten mice each; group I: infected, untreated group; II: infected and treated with albendazole; III: infected and treated with allopurinol; IV: infected and treated with a combination of albendazole and allopurinol.

Mice sacrifice: Mice were slaughtered on day 6 post-infection in experiment I, while in experiment II the mice were sacrificed on day 45 post-infection[17].

Isolation of adult worms and muscle larvae: Adult worms were obtained from the small intestine of infected mice. Overnight starved mice were sacrificed, the entire small intestine was removed, cut into 2-3 cm sections, and placed in a petri dish containing 0.9% saline for 3 h at 37°C. After incubation, adult worms were collected, washed by PBS, and counted under a dissecting microscope[18]. For total larval count, muscles from the tongue, diaphragms and the thorax were removed, weighed and allowed to soak overnight in artificial digestive fluid composed of 100 ml saline, 1 ml concentrated HCl and 1 g pepsin at 37˚C under continuous mixing with a mechanical stirrer. The suspension was filtered then centrifuged at 1,000 rpm for 2 min to sediment the larvae, and count them under the light microscope[18].

Histopathological assessment: Sections of diaphragm muscle of infected mice from different groups were histopathologically prepared[18]. The sections were preserved in 10% formalin, processed and stained by H&E and examined microscopically for the degree of inflammation (mild, moderate, or severe) and other pathological abnormalities[19].

Statistical analysis: We used GraphPad Prism software version 7.00 (La Jolla California USA). Data are expressed as mean±SD. Comparisons between controls and experimental groups were performed using Student's *t*-test. The difference between the experimental groups was significant at $P<0.05$.

Ethical considerations: The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC), Cairo University with approval number CU111F4219. All experimental procedures were conducted in accordance with international guidelines for the care and use of laboratory animals. Proper waste disposal and euthanasia methods were employed as per international legislation. The study adhered to the principles outlined in the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health[20].

RESULTS

Intestinal phase: Table (1) shows significant differences between the treated and control group. Combined treatment exhibited the highest reduction in adult worm count (98.76%), which was statistically similar to the reduction achieved by albendazole alone (98.53%). Both combination therapy, and albendazole monotherapy were significantly more effective than allopurinol alone, which showed a moderate reduction in adult worm burden (69.41%). While the allopurinol group demonstrated a significant reduction compared to the control group, it was less effective than either albendazole alone or the combination treatment in reducing intestinal worm burden.

Muscular Phase: Table (2) shows a significant reduction ($P<0.05$) in larval counts in all the groups under treatment; the maximum reduction of larvae was recorded in the combined therapy. Compared to the control group, the reductions in the larval counts were 93.69% for the tongue, 94.71% for the diaphragm, and 94.52% for the thoracic muscles. Albendazole

treatment alone reduced the larvae by 59.44%, 56.86%, and 57.50%, while allopurinol alone produced reductions of 84.90%, 87.36%, and 83.93% in the same tissues, respectively.

Table 1. Comparison of intestinal adult worm count (Mean ± SD) and percentage of reduction in different treatment groups compared to the control.

Treatment	Adult worm count (Mean ± SD)	% Reduction
Control	88.6 ± 10.46	N/A
Albendazole	1.3 ± 1.16*	98.53
Allopurinol	27.1 ± 9.7*#	69.41
Combined therapy	1.1 ± 0.99*$	98.76

***:** Statistically significant compared to the control group (P<0.05) for Albendazole, Allopurinol, and the combination groups; **#:** Statistically significant; Albendazole group compared with Allopurinol and the combined therapy groups (P<0.05); **$:** Statistically significant; Allopurinol group compared with the combined therapy group (P<0.05).

Histopathological results: The study showed variation in muscle pathology and reduction of larvae in different groups, in response to therapeutic effect of treatments. The muscles of the infected non-treated control mice (Fig. 1a) contained many disseminated larvae. Each larva was encapsulated with a collagenous capsule and surrounded by extensive cellular inflammatory infiltrate. Atrophy, distancing and tearing of muscles were also recorded. Such findings suggest a very sharp pathological reaction to the infection in the absence of any treatment. In contrast, in muscle tissue samples obtained from treated animals either with albendazole (Fig. 1b), allopurinol, (Fig. 1c) or in combination (Fig. 1d), fewer encysted larvae with mild surrounding inflammatory reaction were detected. Muscle sections from mice receiving the combined treatment (Fig. 1d) revealed considerably fewer encysted larvae. Moreover, they showed degenerative changes in their contents and capsules.

Table 2. Comparison of larval counts (Mean±SD) per gram of muscle tissue and the percentage of reduction in different treatment groups compared to the control.

Tissue	Infected	Albendazole		Allopurinol		Combined therapy	
	Mean±SD	Mean±SD	% Reduction	Mean±SD	% Reduction	Mean±SD	% Reduction
Tongue	597.4±130.13	242.3±32.17*	59.44	90.2±10.85*#	84.90	37.7±4.85*#	93.69
Diaphragm	461.3±67.52	199±21.27*	56.86	58.3±9.44*#	87.36	24.4 ± 2.76*#	94.71
Thorax	250.1±45.57	106.3±7.97*	57.50	40.2±4.59*#	83.93	13.7 ± 3.06*#	94.52

***:** Statistically significant compared to control (P<0.05); **#:** Statistically significant compared to Albendazole (P<0.05).

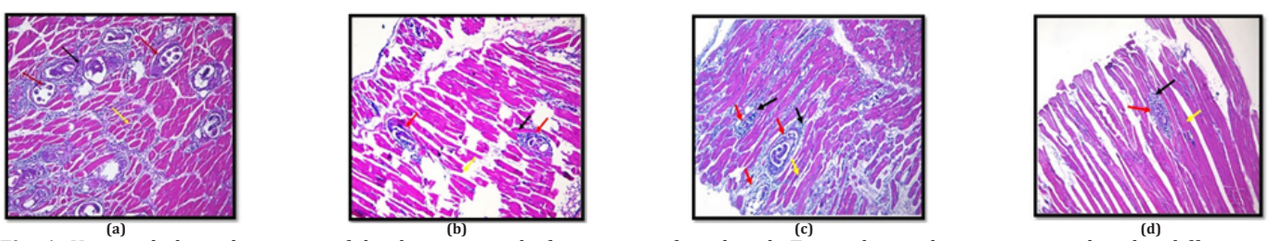

Fig. 1. Histopathological sections of diaphragm muscle from mice infected with *T. spiralis* on chronic stage and under different treatment conditions (H&E stain, x200). **(a)** Untreated mice showing heavy encysted larvae (red arrows) surrounded by intense inflammatory cellular reaction (black arrows), and muscle atrophy (yellow arrow). **(b)** Albendazole-treated mice showing reduction in the number of encysted larvae (red arrow) surrounded by mild inflammatory cellular infiltrate (black arrow) with muscle atrophy and distancing (yellow arrow). **(c)** Allopurinol-treated mice showing reduction in the number of larvae (red arrow) surrounded by dense inflammatory infiltrate (black arrow), and muscle atrophy (yellow arrow). **(d)** Mice treated with combined therapy showing reduction and degeneration in the number of larvae (red arrow) surrounded by mild inflammatory cells (black arrow) with muscle atrophy and distancing (yellow arrow).

DISCUSSION

The present study provides convincing evidence for allopurinol's efficacy in treating trichinosis, singly and in combination with albendazole, using a controlled mouse model. The considerable reduction in numbers of *T. spiralis* in both the intestinal and muscular phases is evidence of the success of these therapies. Our results in the intestinal phase indicate an interesting pattern of effectiveness of different treatments. The reduction rate in the worm counts by the combined therapy (98.76%) is similar to albendazole (98.53%). Allopurinol as a single agent had a much lower rate of reduction (69.41%). It can, therefore, be presumed that the high efficacy of combination therapy against adult worms is due to the action of albendazole, as evidenced by previous studies showing albendazole's effectiveness for the treatment of trichinosis[18,21]. It is worth mentioning that allopurinol alone was significantly more effective in reducing the encysted larvae (83.93-87.36%) as compared to albendazole record of 56.86-59.44%. However, the highest reduction in larval counts (93.69-94.71%) was recorded with the combined therapy. These data show that the efficacy of allopurinol is mostly oriented against the larval stage, whereas that of albendazole is oriented against *T. spiralis* worms. This difference in efficacy at the various life stages of the parasite thus explains the improved overall efficacy of the combination therapy since it would be targeting both intestinal and muscular phases of the infection more completely than either drug alone. The fact

that allopurinol, a drug used mainly in the treatment of gout and hyperuricemia[22], was found to exhibit considerable therapeutic properties against trichinosis is confirmation of recent studies on the repurposing of allopurinol for treating parasitic diseases[10,23].

The mechanism of action of allopurinol in trichinosis, particularly in its synergistic action with albendazole, may be attributed to a set of several metabolic pathways exerted by both drugs affecting *T. spiralis* life cycle stages. Albendazole acts chiefly by binding to β-tubulin, inhibiting microtubule polymerization and causing disruption in *T. spiralis* basic cellular functions[24]. Allopurinol can augment the antiparasitic effect through multifunctional modes. It inhibits xanthine oxidase and reduces the purine substrates available for replication[25,26]. It also may enhance the bioavailability of albendazole through the inhibition of metabolic pathways and thus increase its concentration and efficacy. Although no direct evidence confirms that allopurinol enhances the bioavailability of albendazole, the inhibitory activity of allopurinol on xanthine oxidase was reported to increase the bioavailability of other drugs, e.g., azathioprine and 6-mercaptopurine[27]. This suggests that a similar mechanism may apply to albendazole. Accordingly, both drugs may act synergistically to cause *T. spiralis* oxidative stress. Besides, it acts by inhibiting the enzyme xanthine oxidase, thus reducing reactive oxygen species (ROS) production in the host and enhancing parasite sensitivity to oxidative killing mediated by albendazole. Additionally, it interferes with purine salvage pathways, important for nucleotide homeostasis. This leads to nucleotide starvation, which in turn decreases DNA/RNA synthesis, culminating in parasite death[25].

Therefore, the multi-action of allopurinol, in addition to the disturbance of the microtubules by albendazole, constitutes the improved efficacy of the combined therapy against both phases of trichinosis. Combined treatment emerged as having the greatest consequence on reducing both larval counts and associated tissue damage. This finding agrees with the concept of drug interaction, which was recently advocated in antiparasitic chemotherapy[18,28]. This, in fact, follows the literature from other studies where combination therapies result in additive and synergistic effects which enhance the therapeutic efficacy of drugs[18,29-32]. These studies concluded that a combination of different anthelmintics results in a better outcome by reducing parasite burdens and inflammation compared to single therapies.

Histopathological examination of muscle sections treated with combined therapy also revealed that the number of encysted larvae was remarkably reduced. Remaining larvae also showed significant degenerative changes both in their contents and capsules. This finding confirms that, apart from a significant reduction of the larval burden, there was some degeneration in the surviving larvae, further reducing their capacity to cause muscle damage. These findings indeed point to the fact that albendazole in combination with allopurinol may be a promising new therapeutic intervention against muscular trichinosis, notably in endemic regions where the disease causes serious public health hazards. Moreover, our findings contribute to the growing literature on drug repurposing which is a promising strategy for accelerating drug discovery and development by finding new valuable indications for existing drugs[33,34].

In conclusion, our study shows that allopurinol, whether administered alone or in combination with albendazole, is actually an effective therapeutic agent against muscular trichinosis in the mouse model. Future studies are recommended using other animal models, followed by human clinical trials to establish an ideal dosing for maximum therapeutic benefit while minimizing the risk of potential side effects. Besides, the mechanism by which allopurinol acts, particularly in combination with albendazole, needs to be established.

Author contribution: The idea and design of the study, the practical work, the interpretation of the findings, the statistical analysis, and the writing were all contributed to by the authors.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding statement: The authors have no funding to report.

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