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Examining the Angiogenic and Antioxidant Effects of Various Paracetamol Dosages Using a Chorioallantoic Membrane Model

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Abstract

Introduction: Paracetamol is one of the most popular and frequently used analgesic and antipyretic medications in the world. It was aimed at investigating the effects of paracetamol on angiogenesis and oxidative stress markers in the in vivo chorioallantoic membrane model (CAM).

Materials and Methods: The 40 fertilized chick eggs were used in the experiment. The four groups were as; the control group (n = 10), 10^{-6} M bevacizumab group (n = 10), 10^{-4} M paracetamol group (n = 10) and 10^{-5} M paracetamol group (n = 10). Stereoscopic microscopy was used to assess angiogenesis on the window that was opened on the eggshell. Total oxidant capacity (TOS), total antioxidant capacity (TAS), and oxidative stress index (OSI) were analyzed in albumen specimens. The scoring methodology described in earlier research publications was used to determine and compare the average score values. One-way analysis of variance and the post hoc Tukey test were performed to assess oxidative stress markers between the groups.

Results: The bevacizumab group demonstrated a strong anti-angiogenic effect, but the control group and both paracetamol groups showed no anti-angiogenic effect. Paracetamol increased TAS values at a 10^{-4} M concentration. The bevacizumab group's TOS and OSI values were significantly higher compared to the control group.

Conclusion: Paracetamol is used by a lot of people; healthy blood vessel growth and the balance between oxidants and antioxidants are important. The important result of this study is that paracetamol has strong antioxidant effects and no anti-angiogenic effects.

Key words: paracetamol; chorioallantoic membrane; angiogenesis; oxidative stress markers.

Introduction

With a molecular weight of 151.16 g/mol, paracetamol(4-hydroxyacetanilide, acetaminophen) is a member of the 4-aminophenol phenol class and is one of the most popular and frequently used analgesic and antipyretic medications in the world (1). The chemical is known as a cyclooxygenase 1 inhibitor, a cyclooxygenase 2 inhibitor, an antipyretic, a non-steroidal anti-inflammatory drug, a hepatotoxic agent, a ferroptosis inducer, and a non-narcotic analgesic (1, 2). When used at therapeutic levels, paracetamol appears to be safe, but greater doses can cause renal and/or hepatic damage in both people and experimental animals (3). A healthy equilibrium between antioxidants and free radicals is essential for proper physiological function. An important role that oxidative stress plays in mediating pathophysiological events may be linked to the etiology of multiple illnesses, including diabetes mellitus, atherosclerosis, cancer, and inflammatory diseases. Paracetamol, as a phenol derivative, exhibits antioxidant action in a variety of biological models of lipid peroxidation (4). A recombinant humanized monoclonal immunoglobulin G antibody called bevacizumab prevents vascular endothelial growth factor-A (VEGF-A) from adhering itself to endothelial cells (5). For this reason, it is preferred in experimental studies examining vascular connection development. A popular model for the investigation of angiogenesis and medication effects is the chick chorioallantoic membrane (CAM) (6). Because of its broad vascularization and ease of access (7), it is the favored material for use in experimental research. The impact of paracetamol on oxidative stress and angiogenesis in the chorioallantoic membrane (CAM) remains inadequately researched. The aim of the current study was to examine how paracetamol affected angiogenesis and oxidative stress in the experimental CAM model.

Material and Methods

Every stage of the experiment was in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals. This model does not necessitate any requirements for

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animal protocol or ethical approval and patient consent. This research was conducted in a multidisciplinary laboratory at the Mardin Artuklu University Faculty of Medicine.

Cam: The researchers used Ross 308 chick eggs (n = 80) and discarded 40 eggs that were unfertilized, partially developed, deceased, or deformed. A total of 40 remaining embryos were divided into four groups. Figures 1 and 2 illustrate the phases of the investigation.

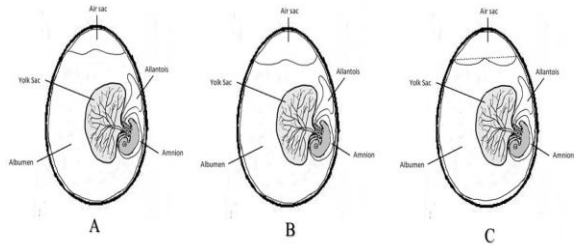

Figure 1: Embryo Status in Experimental Model Stages. (A) An embryo, an air sac, amniotic fluid, and albumen are all present in a typical chick egg. (B) The enlarged air sac following albumen extraction. (C) Removing the egg shell from the dashed line to track embryonic development (Source: authors-made drawings.)

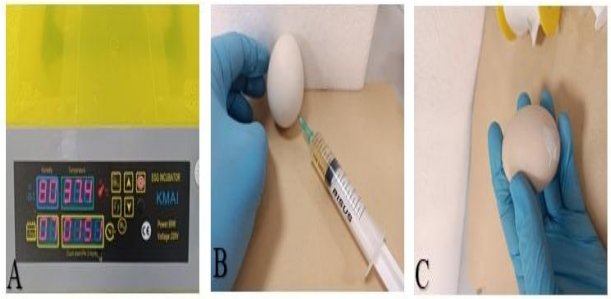

Figure 2: Fertilized chick eggs were placed in an incubator. (A), albumen was extracted using a syringe (B), and the eggs were sealed with an elastic medical flaster. (Source: the authors' own elaboration).

We sanitized the fertilized chicken eggs with 70% alcohol and placed them in the incubator at 37.4°C and 80% humidity (Figure 2A). A sample of 4-5 cc of albumen was taken from the bottom of each egg on the third day of incubation (Figure 2B), which gave the embryo greater room, and before the eggs were placed back in the incubator, they were sealed with medical elastic plaster (Figure 2C). On the fifth day, the window was opened on the eggshell by micro forceps, and the pellets were implanted in the embryos. The embryos' vascular densities were assessed on the eighth day of incubation, as previously mentioned (7, 8). Using a syringe, 4–5 mL of albumen was extracted to measure post-application oxidative stress markers following the assessment of vascular development on the eighth day.

Procedures for grouping and administering medications: Research on experimental in vivo modeling should, whenever possible, be conducted using a small number of samples. The number of eggs in each group was calculated using previously published research (7-9). The present experiment was designed, mimicking the concentrations of the drug attained in plasma, as no effect of paracetamol was observed at doses below 10^{-5} M (10, 11). Two medication concentrations linked to therapeutic levels (10^{-5} and 10^{-4} M) were utilized (10, 11). The grouping procedure followed these steps: Control group (n = 10): The embryos, which served as a model for typical vascular development, were given drug-non-containing pellets. Group bevacizumab (BC), (n = 10): On the fifth day of incubation, the embryos received pellets implanted containing 10^{-6} M bevacizumab (CAS number: 216974-75-3). Group Paracetamol (PC) 10^{-4} (n = 10): The embryos received pellets implanted with 10^{-4} M paracetamol (IUPAC number: N-(4-hydroxyphenyl) acetamide, N-(4-hydroxyphenyl) ethanamide) during the fifth incubation day. Paracetamol was dissolved in 3% hot agarose gel and converted into pellet form (12). Group PC 10^{-5} (n = 10): The embryos received pellets implanted with 10^{-5} M paracetamol (IUPAC number: N-(4-hydroxyphenyl) acetamide, N-(4-hydroxyphenyl) ethanamide) during the fifth incubation day. Paracetamol was dissolved in 3% hot agarose gel and converted into pellet form (12).

Scores for angiogenesis: Under a stereoscopic microscope, the embryo's vascular development and the impact of drug-containing or non-containing pellets on the capillary network were assessed. Photos were taken of the areas, and the capillary extent was measured after three days (on the eighth day) after the drug was applied (Figure 3). The extension of neovascularity and the creation of new vessels from the embryo's main branches were assessed (7, 8, 13). The formula to calculate the average score is: ([the number of embryos (score 1) × 1] + [the number of embryos (score 2) × 2]) / the total number of embryos (14). Averaging less than 0.5 indicates no anti-angiogenic effect, 0.5 to 1 indicates a weak anti-angiogenic effect, and >1 indicates a strong anti-angiogenic effect (14).

Measurement of oxidative stress markers: The albumen samples taken three days after pellet implementation (on the eighth day) were used to quantify the markers of oxidative stress. The modified Erel method was utilized to evaluate the total oxidant status (TOS) and total antioxidant status (TAS) using a colorimetric commercial kit

(Rel Assay, Mega Tip, Gaziantep, Turkey). The catalog and lot numbers of the TAS and TOS kits were RL0024 and RL0017, respectively. The upper limits of the linearity of the TAS and TOS assays were 6.0 mmoL Trolox equiv./ L and 200 µmol H_2O_2 equiv./L, respectively. Limits of detection of the TAS and TOS assays were 0.09 mmoL Trolox equiv./L TAS and 1.13 µmol H_2O_2 equiv./L, respectively. The following formula was used to determine the oxidative stress index (OSI) values: OSI = TOS (mmoL H_2O_2 equiv./L)/TAS(mmoL Trolox equiv./L), (7).

Statistical analysis: The scoring methodology described in earlier research publications was used to determine and compare the average score values (7-9, 13, 14). The continuous variables were represented by the mean and standard deviation. The analyses using the Shapiro-Wilk and Kolmogorov-Smirnov tests demonstrated that the data have shown normal distribution (p>0.05). Tukey's test was performed as a post-hoc test after the one-way analysis of variance (ANOVA) test was used to assess oxidative stress markers between the groups. The data was analyzed by the IBM Statistics SPSS version 22.0 program. A statistically significant p-value was defined as less than 0.05.

Table 1: Presenting the anti-angiogenic scores of the groups using the previously reported anti-angiogenic scoring method (8, 9–12).

	Scores				
	0	0.5	1	2	Avarage score
Control (n=10)	9	1	0	0	0
Paracetamol 10^{-4} M (n=10)	8	2	0	0	0
Paracetamol 10^{-5} M (n=10)	7	3	0	0	0
Bevacizumab 10^{-6} M (n=10)	0	1	5	4	1.3

Average score < 0.5: no anti-angiogenic effect, 0.5- 1 = weak anti-angiogenic effect, >1 strong anti-angiogenic effect.

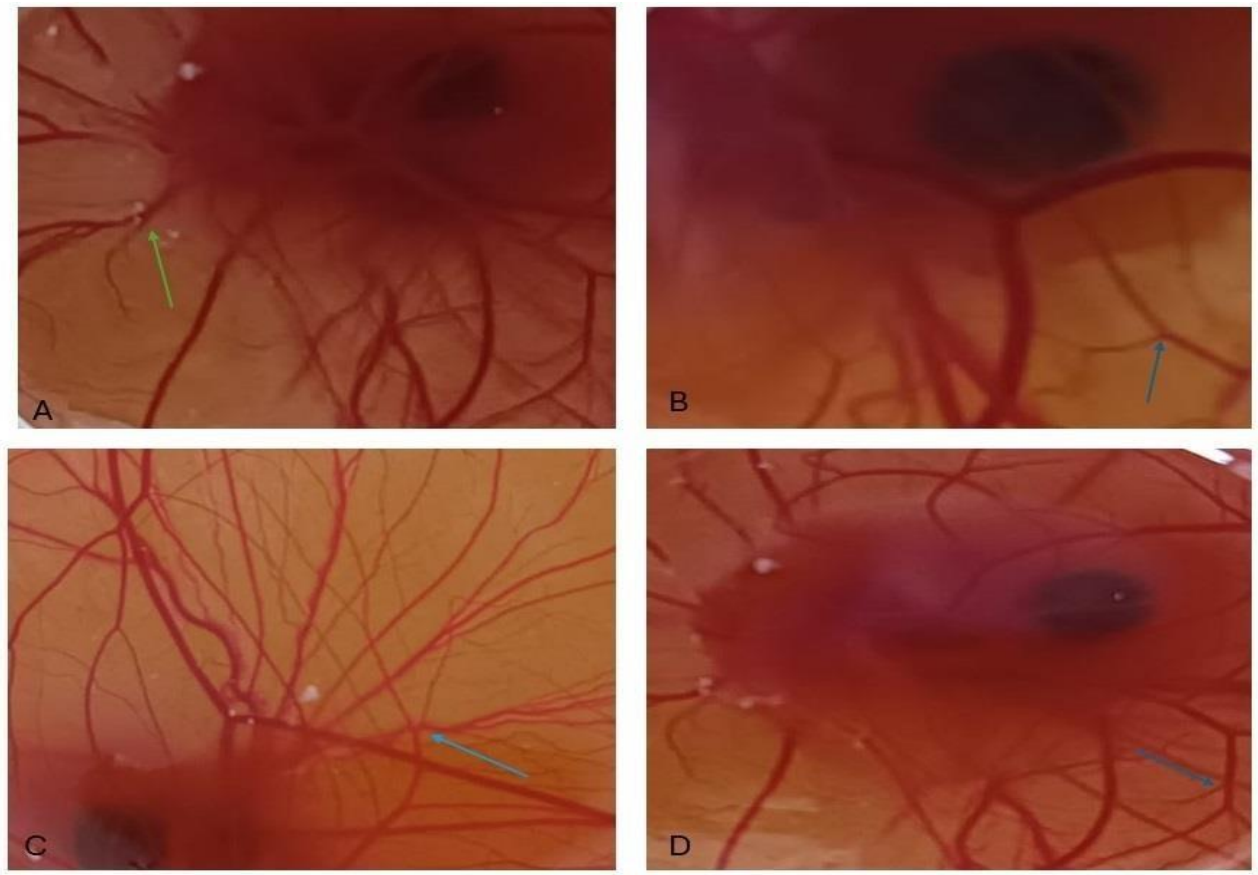

Figure 3: Images of groups' angiogenesis. (A) Following free pellet implantation, a vascular network formation (well-developed vascularity), (control group); (B) The supression of the growth of the vascular network following 10^{-6} M bevacizumab pellet implantation (score 1.3); (C) The development of a vascular network after the implantation of 10^{-4} M paracetamol pellets (well-developed vascularity, score 0). (D); the development of a vascular network after the implantation of 10^{-5} M paracetamol pellets (well-developed vascularity, score 0), Average score < 0.5: no anti-angiogenic effect, 0.5- 1 = weak anti-angiogenic effect, >1 strong anti-angiogenic effect. (Source: the autors' own elaboration).

Results

The BC group demonstrated a strong anti-angiogenic effect (average score 1.3), but the control group, PC $10^{-4,}$ and PC 10^{-5} groups showed no anti-angiogenic effect based on the average score values (average score 0), (Table 1, Figure 3). Table 2 displays the findings of the ANOVA analyses of the TAS, TOS, and OSI values for the research groups. Paracetamol significantly increased TAS values at a 10^{-4} M concentration (p = 0.04). The TAS values of the PC 10^{-5} and BC groups were not different from the control group ($p \geq 0.05$). There were no notable differences in TOS and OSI values among the control, PC 10^{-4}, and PC 10^{-5} groups ($p > 0.05$). The BC group's TOS and OSI values were significantly higher compared to the control group ($p<0.001$; $p<0.001$, respectively).

Table 2: The groups' values for total antioxidant status, total oxidant capacity, and oxidative stress index.

	Groups				*p* value by one-way ANOVA test
	Control (n=10)	Bevacizumab (n=10)	10^{-4} PC (n=10)	10^{-5} PC (n=10)	
TOS (mmol/L)	6.39±1.44[b]	13.52±2.57[a,c,d]	6.21±1.09[a]	6.60±1.58[b]	<0.001
TAS (mmol/L)	1.10±0.21[c]	1.01±0.28[c,d]	1.68±0.65[a,b]	1.66±0.55[b]	0.002
OSI (TOS/TAS)	6.11±2.44[b]	14.17±4.09[a,c,d]	4.16±1.51[b]	4.48±2.15[b]	<0.001

The values expressed as mean ± standard deviation; TOS: total oxidative capacity; TAS: total antioxidant capacity; OSI: oxidative stress index. [a, b, c, d]: Different letters in the same row indicate statistically significant differences between the groups ($p < 0.05$ by post-hoc Tukey tests). [a] vs. the control group; [b] vs. the Bevacizumab group; [c] vs. the 10^{-4} PC group; [d] vs. the 10^{-4} PC group.

Discussion

Paracetamol is one of the world's most widely used and well-liked analgesic and antipyretic medications (1). The studies on the CAM model that investigate paracetamol's anti-angiogenic effect and oxidant-antioxidant balance are limited.

The present study indicates that some doses of paracetamol increased antioxidants in an experimental manner. At different dosages, paracetamol did not exhibit anti-angiogenic qualities, according to our findings. These research findings are among the first to show paracetamol's effect on angiogenesis and oxidative stress markers at varying concentrations using the CAM model. It was reported that paracetamol showed antioxidant properties in a study conducted on erythrocytes on catalase inhibition and H2O2-forced erythrocytic membrane lipid peroxidation (4). Paracetamol, as a phenol derivative, exhibits antioxidant activity in a variety of biological models involving lipid peroxidation (4). These effects could be explained by phenol and acetamide, since they are electron-donating groups for paracetamol (4). Rats exposed to high doses of paracetamol showed an increase in OSI values in their brain and liver (15). It is well known that high dosages of paracetamol can result in severe hepatic necrosis in both humans and animals because the drug can interacts with cytochrome P-450 peroxidases, which are responsible for the production of quinones and semiquinones (4). Furthermore, it has been shown that one of the main effects of paracetamol toxicity is the depletion of cellular glutathione, a molecule necessary for the termination stage of lipid peroxidation as antioxidant defense (16). The dosage of a drug has a significant impact on how it acts. The CAM model is the most popular method used as an in vivo angiogenesis model in numerous studies because of its many advantages (14, 17–20). Instead of using animal models, the highly vascularized extraembryonic chorioallantoic membrane of fertilized chicken eggs is a simple, easy-to-reach, and cheap way to test for angiogenic potential. Its advantages include faster results than animal models, direct access to the vascular system free from maternal metabolic or hormonal consequences, and the ability to observe the study's outcomes through light or electron microscopy (14). Moreover, the CAM model is one of the most similar to an animal experiment in that it preserves both the embryo and the membrane structure. Since most countries do not consider a chick embryo to be a living animal until day 17 of development, the CAM does not require administrative procedures to acquire ethics committee approval for animal testing (18). The

main drawback of CAM is that it already has a fully formed vascular network, making it difficult to discern the test substance's effects from the vasodilation that inevitably results from its treatment. A non-specific inflammatory response is an additional restriction. Doing the study in the early stages, when the host's immune system has not yet finished developing, can prevent the aforementioned drawback (8, 21). Angiogenesis, the intricate process of creating new blood vessels, is crucial for healthy growth and development, the regeneration of tissues and organs, and a variety of pathological disorders (22). VEGF is a key molecule that initiates angiogenesis and controls neovascularization. Bevacizumab is a recombinant humanized immunoglobulin G1 monoclonal antibody that is made in Chinese hamster ovary cells utilizing DNA technology. Bevacizumab inhibits angiogenesis by blocking VEGF from attaching to its receptors (KDR and Flt-1) on the surface of endothelial cells (23, 24). Previous studies have demonstrated the anti-angiogenic effects of bevacizumab in the CAM model (16, 25). In the current study, we observed that bevacizumab has antiangiogenic effects. In the present experiment, paracetamol had no anti-angiogenic effect. Angiogenesis and vascular remodeling genes were found to be suppressed by paracetamol in a study using trophoblast cell culture (26). However, the mentioned study examined gene expression rather than angiogenesis scoring. According to Lee et al., paracetamol exhibited a moderate degree of antiangiogenic activity (27). Nevertheless, the aforementioned study had a different methodology. The drug's effects may vary depending on the concentration of the drug, the type of sample applied, and the application method. Oxygen-breathing organisms continually produce oxygen radicals as a result of their metabolism. In biological organisms, oxygen-derived free radicals are the most significant type of radical. Superoxide radicals, hydrogen peroxide, and hydroxyl radicals are produced when oxygen is reduced by each obtaining an electron. These molecules possess unique chemical features due to the unpaired electron(s), such as the ability to remove electrons from other compounds in order to achieve stability. The antioxidant system functions as a whole to neutralize free radicals, which are constantly forming and posing a threat to the organism's survival (28). Oxidative stress refers to the state of oxidative damage that arises when the essential balance between the creation of free radicals and antioxidant defenses is unfavorable. Even though it is commonly acknowledged that their causes are multifaceted, oxidative stress is a common denominator throughout many chronic diseases (28, 29). Some of the most important antioxidants in humans are paraoxonase, glutathione, glutathione peroxidase, glutathione S-transferase, paraoxonase, and small molecular weight antioxidants like vitamins C and E, flavonoids, carotenoids, melatonin, ergothioneine, and others (28, 30). The present study's findings demonstrate that exposure to some paracetamol dosages increased the antioxidants ($p = 0.04$). Additional research has confirmed the antioxidant effect of paracetamol, which corroborates our findings (4). Earlier studies have demonstrated the opposite effects at toxic doses of the drug (15, 16). The drug's dose-dependent action could explain this variation in outcomes. Physiological angiogenesis is a critical process for embryonic development and is ongoing throughout many processes, including the ovarian and endometrial cycles and wound healing. The fact that paracetamol does not have negative effects on angiogenesis and oxidative stress can help explain some of the features of paracetamol for the mentioned processes that increase drug safety and reduce side effects. We think that in vivo studies in which various paracetamol dosages are applied, covering a wider dose range, and metabolic pathways are included are needed, which may shed more light on this issue.

Study Limitations: Because the structure of the chicken CAM differs from mammalian tissues and drug metabolism varies across species, the findings may have limited relevance to humans. Because the experimental durations in CAM models are short, long-term effects cannot be studied. These limitations should be considered when designing experiments and analyzing data using the CAM model.

Conclusion

Among the most widely used analgesics is paracetamol. As there isn't adequate research demonstrating paracetamol's antioxidant or antiangiogenic effects in the CAM model, the novel findings in this study are beneficial. Since paracetamol is used by many people and healthy blood vessel growth and a balance between oxidants and antioxidants are important during pregnancy, the fact that the drug doesn't affect angiogenesis or make oxidative stress worse supports the idea that it is safe in this situation.

Ethics approval: In this study, all necessary ethical rules and legislation in our country and internationally were followed. In Turkey, where the study was conducted, considering the developmental stages of chicken embryos, ethical committee permission and experimental animals are not legally required for experiments in the first 14 days of the embryo. The study was terminated on the 8th day of incubation. These experiments can be performed in any laboratory and in a suitable incubator. Based on this decision, all studies were conducted by taking into account animal welfare and rights and by complying with ethical rules.

Competing interests: Authors declared no conflict of interest.

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Authors' contributions: HBS and TB made a significant contribution to the work reported, took part in drafting, revising, or critically reviewing the article. HBS and TB gave the final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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