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Comparison Study of Montelukast with Dexamethasone for Possible Protection against Lipopolysaccharide-Induced Oxidative Damage in Bone Marrow of Albino Male Mice

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Abstract

Oxidative stress arises when the host defensive mechanisms of anti-oxidants cannot withstand the vicious attack made by numerous reactive oxygen and nitrogen species. This prooxidant-antioxidant imbalance can cause endocrine, cardiovascular, pulmonary, and neurological disorders. In sepsis, this imbalance promotes organ failure, including bone marrow. The aim is to evaluate the anti-oxidant effect of montelukast compared with dexamethasone against lipopolysaccharide (LPS)-induced oxidative stress in the bone marrow. Twenty-eight male Albino mice were randomly divided into four groups of seven each. Group I (control) received distilled water by oral gavage once a day for a week and euthanized on the 8th day; Group II (induction) received a single intraperitoneal injection of LPS 10 mg/kg and euthanized on the 2nd day. Group III received oral gavage dexamethasone 2.5 mg/kg once a day for a week, then two hours after the final dose, LPS was given and euthanized on the 8th day. Group IV received oral gavage montelukast 20 mg/kg once a day for a week, then two hours after the final dose, LPS was given and euthanized on the 8th day. Results showed that the LPS-model group had significantly higher malondialdehyde and myeloperoxidase levels than the control group. Pretreatment with dexamethasone (group III) and montelukast (group IV) significantly lowers both values. In bone marrow histopathology, montelukast reduced inflammatory cells. In conclusion; Montelukast may be a promising anti-oxidant and a medication to prevent oxidative stress consequences in humans.

Keywords: Dexamethasone, Lipopolysaccharide, Montelukast, Oxidative Stress, Sepsis.

Introduction

Sepsis is a life-threatening immune-inflammatory disturbance that occurs due to direct exposure to pathogenic insults such as gram-negative bacteria like *Escherichia. Coli*, or their pathogen-associated molecular patterns (PAMPs), such as flagellin or LPS [(1)]. Cytokine storms and reactive oxygen-nitrogen bursts are the main features of this syndrome [(2,3)]. The pathophysiology of sepsis starts with recognizing pathogen-derived molecular patterns (endo- and exotoxins, lipids, or DNA sequences) or damage-associated molecular patterns (DAMPs). These molecules activate specific Toll-like receptors (TLRs) on the surface of antigen-presenting cells (APCs) and monocytes, initiating the clinical syndrome of sepsis by transcription of genes involved in inflammation and adaptive immunity [(4)]. The binding of PAMPs and DAMPs to TLRs on APCs and monocytes leads to signal transduction and nuclear factor kappa-light-chain – enhancer of activated B cells (NF - κB) translocation into the cell nucleus. This triggers the expression of "early activation genes" such as pro-inflammatory interleukins (IL) such as IL-1, IL-12, tumor necrosis factor-alpha (TNF-α), and interferons (IFNs). These activate other cytokines (e.g., IFNs, IL-6, IL 8), complement and coagulation pathways, and downregulate adaptive immune system components by negative feedback [(5)]; During early septic illness, pro-inflammatory and anti-inflammatory cytokines increase [(6)].

Through emergency granulocyte maturation, severe bacterial infections release mature and immature neutrophils from the bone marrow; moreover, the immature form spontaneously produces and releases neutrophil extracellular traps (NETs) and has impaired phagocytosis and oxidative burst capacity [(7)]. Increased occurrence of NETs is associated with hyper-coagulation and endothelial damage [(8)].

When phagocytosis is not feasible, neutrophils employ de-condensed chromatin with granular and nuclear proteins such as myeloperoxidase (MPO), neutrophil elastase (NE), and proteinase-3 to immobilize gram-negative and positive bacteria [9]. The release of NETs is known to be triggered by, for instance, cytokines and chemokines, as well as platelet agonists like thrombin and ADP [10]. In a short-term LPS administration, lipid peroxidation (LP) (presented as malondialdehyde assay) is increased in mice's brain and liver [3]. Lipopolysaccharide increases inflammatory cytokines, including TNF-α and IL-6, leading to higher ROS generation through direct or indirect activation of oxidative enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [11,12]. Direct causes include mitochondrial and peroxisomal dysfunction [13,14]. Thus, free radicals have a dual role in many physiological and pathological circumstances [15]. Low to moderate reactive oxygen and nitrogen species are needed for cellular development and can be considered as a host defensive mechanism. To defend against pathogens, phagocytes (neutrophils, macrophages, monocytes) emit free radicals [16]. At high concentrations, detrimental processes can damage cell membranes, carbohydrates, proteins, lipids, lipoproteins, and DNA [16]. Peroxidation by excess hydroxyl radicals damages cell membranes and lipoproteins. MDA, a cytotoxic and mutagenic compound, results from this interaction. Polyunsaturated fatty acids (PUFAs) like arachidonic acid react with ROS to produce reactive aldehydes, including MDA, causing lipid peroxidation [17]. Malondialdehyde levels were increased regardless of site of infection, type of microorganism, or dysfunctional organ system, suggesting that lipid peroxidation was a host response rather than a pathogen- or organ-specific reaction and should be used to measure ROSs' devastating effect [18].

Mitochondria is a primary source of intracellular ROS because the incomplete reduction of oxygen to water through the electron transport chain produces superoxide and hydrogen peroxide [19]. Uncoupled oxidative phosphorylation and depleted anti-oxidant stores in sepsis are postulated mechanisms that enhance ROS burden [20].

As second messengers, free radicals ROS activate NF-κB and the activator protein-1 (AP-1), leading to the transcriptional activation of pro-inflammatory genes, including TNF-α and IL-6. Furthermore, the mitochondrial ROS inhibitors diminish LPS-induced IL-6 and hinder MAP kinases [21,22]. In turn, cytokines such as TNF-α and IL-6 can increase free radical levels by promoting monocyte chemoattractant protein-1 (MCP-1) production which attracts monocytes, memory T cells, and dendritic cells to tissue injury and infection sites [23].,

Myeloperoxidase (MPO) is a key component of neutrophils, creating and maintaining an alkaline environment that fights bacteria in freshly formed phagosomes. Myeloperoxidase is required by neutrophil extracellular traps (NETs) [24]. Partial MPO deficiency or pharmacological MPO inhibition delays and diminishes NET production, indicating that this process requires MPO translocation to the appropriate subcellular compartment [25].

Fine coordination is required between many biochemical pathways, such as neutrophil activation, ROS formation by superoxide-generating NADPH oxidase, and MPO release by exocytosis [26]. All of these coordinated reactions result in the eradication of the bacterial invasion. Invading bacteria use superoxide dismutase (SOD) to produce H_2O_2, which is consumed by MPO for chloride oxidation to produce chloramine and hypochlorite and these products are highly toxic to the invading bacteria. Ceruloplasmin regulates myeloperoxidase activity, and this relationship significantly limits MPO's halogenating and peroxidase activity [27].

Dexamethasone is a synthetic glucocorticoid frequently utilized in clinical settings due to its powerful anti-inflammatory and immunosuppressive properties. Its mode of action showed immediate impacts of corticosteroids including reduced vasodilation and permeability of capillaries, enhanced stability of lysosomal membranes [28], and decreased migration of leukocytes to areas of inflammation [29], and this may contribute to decreased oxidative stress. Dexamethasone facilitates alterations in gene expression, resulting in a variety of subsequent consequences that occur over hours to days [29]. Unfortunately, dexamethasone has many adverse effects like hypertension, diabetes, atherosclerosis, and myopathy due to overproduction of ROS leading to mitochondrial and endothelial dysfunction [30].

Montelukast is an oral leukotriene receptor antagonist with anti-inflammatory and antioxidant properties that bind with high affinity and selectivity to the cysteinyl leukotriene receptor 1(CysLT type 1) receptor and, hence, antagonizes the physiological actions of LTC4, LTD4, and LTE4 at the receptor site; besides, the NF-κB suppression by high dosages of montelukast regulates IL-6, TNF-α, and MCP-1 production [31]. Moreover, it slows chondrocyte senescence caused by TNF-α [32].

Aim of the study

The study was designed to determine the possible protective effect of montelukast in comparison with dexamethasone on mice bone

marrow utilizing measurement of the following parameters: **(1)** Bone marrow MDA measurement by competitive ELISA technique. **(2)** Bone marrow MPO measurement by sandwich ELISA technique. **(3)** Histopathological bone marrow sections for each experimental group to evaluate tissue alterations by focusing on cellularity, adipose, and inflammatory changes.

Materials and Methods

Chemicals and reagents

Sigma Aldrich-Germany supplied LPS endotoxin from *Escherichia. Coli* serotype O55:B5. Dexamethasone raw powder was from Sammara-Iraq while montelukast raw powder was from Pioneer-Iraq. In this study, two kits were used. Myeloperoxidase was measured using a sandwich ELISA kit that was purchased from Cloud-Clone Crop®-USA. Malondialdehyde was measured using a competitive ELISA kit that was purchased from Elabscience®-USA. A PH=7.4 phosphate buffer saline liquid was purchased from Elabscience® USA. The Baghdad Pharmacy College medical store was provided buffered formalin 10% and Di-ethyl-ether Scharlau-Spain.

Experimental animals

The Animal house of the College of Pharmacy/University of Baghdad provided 28 Albino male mice weighing 30–45g; and, four (4) groups of mice were caged at ambient humidity, temperature (25°C), and light/dark cycle with free access to commercial pellets and water. Seven (7) mice in each group were randomly assigned to four groups and given the following:(1) Control group: Mice received 0.25-0.5 ml of distilled water by oral gavage once daily for a week and then were euthanized on day eight. (2) LPS-model group: Mice received a single IP injection of LPS (10mg/kg) and were euthanized the next day [42]. (3) DEX-LPS group: Mice received dexamethasone (2.5 mg/kg) oral gavage once daily for a week, then LPS (10mg/kg) was given IP after two hours; and, on day 8, mice were euthanized [42]. (4) MONT-LPS group: Mice received montelukast (20 mg/kg) by oral gavage once daily for a week, then LPS (10mg/kg) was given IP after two hours; and, on day 8, mice were euthanized [36].

Femur bone excision and bone marrow isolation

After anesthesia with diethyl ether in a closed glass jar for all animals in each group, femur bones were excised, and muscle fibers were removed. Then, the femur was rinsed with PBS, and a sterile disposable needle of two sizes (3ml and 1ml syringes) was attached to both ends and twisted to make two holes. An insulin syringe was used to withdraw 20-25 units of cold phosphate buffer saline solution (PBS) of PH=7.4 and inject it in the hole of one femur end, flushing the bone marrow many times until it emerged with PBS from the other end and became clumped in the Eppendorf tube. Then, centrifuge the tube at 2000 rpm for 5 minutes at 4°C. The micropipette draws PBS from the tube. Samples are stored at -20°C until bone marrow biomarker estimation [33].

Preparation of bone marrow for histopathologic studies

Whole femurs were immersed in a 10% neutral buffered formalin (10% NBF) solution at room temperature until further processing. For femur decalcification, they were removed from the fixative (10% NBF) and immersed in 5-10% nitric acid [34].

Histopathological evaluation of bone marrow tissue damage

Bone marrow tissue damage was scored utilizing the following parameters, cellularity, adiposity, and inflammation. A three-point scale was recorded for each parameter; For instance, hypocellular bone marrow records (1), fatty bone marrow records (3), and damage due to inflammatory process was progressive in the score (3). The slides were examined under the power (x40) and (x100) by a specialized pathologist (Table 2).

Enzyme-linked immunosorbent assay

The Sandwich ELISA method can be used to measure myeloperoxidase (MPO) levels, briefly; the samples were added and incubated in the anti-mice MPO monoclonal antibody pre-coated wells of the kit plate for 30-60 minutes and then rinsed to remove the unbounded substances. A biotinylated detection antibody was then added and incubated, then washed; horseradish peroxidase (HRP) with avidin conjugate was added, and in another washing step, tetramethylbenzidine (TMB) substrate for the HRP was added. Under the effect of peroxidase, a blue intermediate is formed and converted to yellow color by the action of STOP solution. The intensity of color correlated to the quantity of MPO in bone marrow tissue and was spectrophotometrically measured at 450nm by a microplate reader. In the case of ELISA competitive analysis of MDA, instead of using a biotin antibody in this instance, a synthetic MDA conjugate was employed, and one antigen-antibody binding site was utilized rather than two. In the sandwich method, color intensity is directly correlated with antigen concentration while in the competitive ELISA, intense color indicates low antigen concentration.

Statistical analysis

A statistical package for the social science version 25 was used to analyze the data. A normality test was done to determine if sample data were normally distributed. Results were analyzed as mean ± standard error using one-way analysis of variance (ANOVA) and post hoc Tukey multiple

comparisons for normally distributed values. Group differences were judged significant when the P-value was (p<0.05).

Results

Effect on bone marrow malondialdehyde MDA

Bone marrow MDA measurement revealed a significant elevation (p<0.05) in group II of mice that received LPS intraperitoneally compared with the control group. Moreover; pretreatment with dexamethasone and montelukast (group III and group IV, respectively) revealed a significant reduction (p<0.05) in bone marrow MDA compared with the LPS-model group. However, the levels of MDA did not reach the baseline values of the control group (normalization did not occur). Table 1. Figure (1-A)

Effect on bone marrow myeloperoxidase MPO

Bone marrow MPO measurement revealed a significant elevation (p<0.05) in group II of mice that received LPS intraperitoneally, compared with the control group. Furthermore; pretreatment with dexamethasone and montelukast (group III and group IV, respectively) revealed a significant reduction (p<0.05) in bone marrow MPO compared with the LPS-model group. However, bone marrow MPO levels did not reach the baseline values of the control group in the case of group III. While with group IV, normalization occurred. Table 1. Figure (1-B).

Table 1. Effects on bone marrow MDA and MPO among groups.

Group/Parameter	MDA	MPO
Control	166.087 ± 1.665	566.799 ± 12.457
LPS model	589.948 ± 10.715 *	3021.821 ± 92.146 *
DEX-LPS	229.122 ± 0.739 #+	1042.678 ± 44.639 #
MONT-LPS	307.033 ± 4.644~	565.680 ± 31.659 ~+

Values presented as mean ± SEM, (N=7) for each group. * denotes significant elevation compared with the control group (p<0.05); # and ~ denote significant reduction compared with the LPS group (p<0.05); + denotes the advantage of one of these two drugs.

Table 2. Histopathological scoring according to presented slides results.

Parameter	Control	LPS	DEX-LPS	MONT-LPS
Cellularity	3	1	1	2
Adiposity	1	2	2	1
Inflammation	0	2	1	1

Cellularity gets better when scores increase. Adipose tissues increased when scores increased. Inflammation is present from score 1 and gets worse when the score increases.

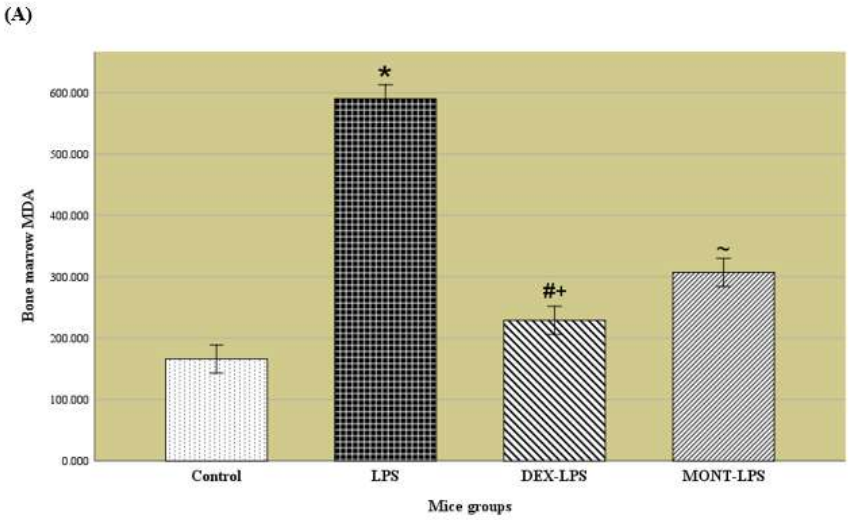
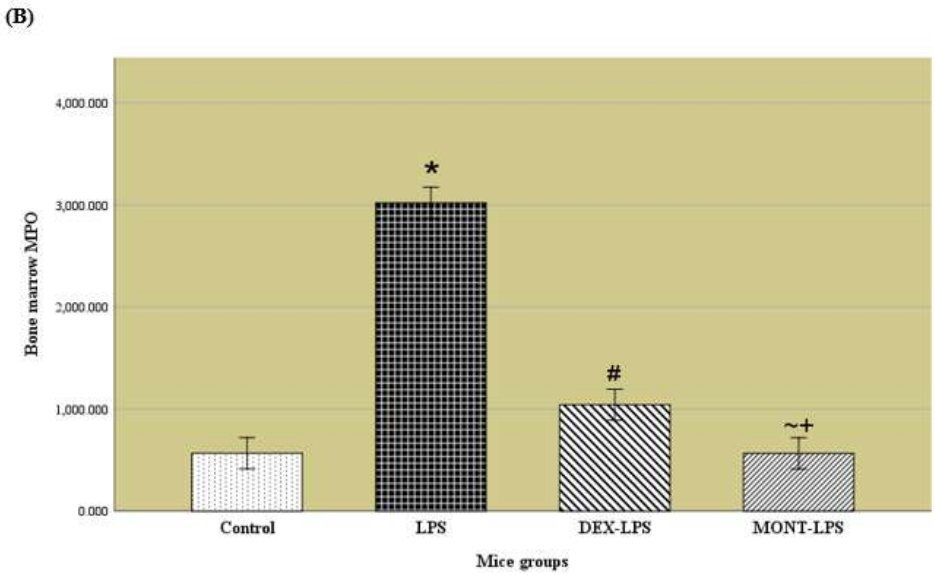
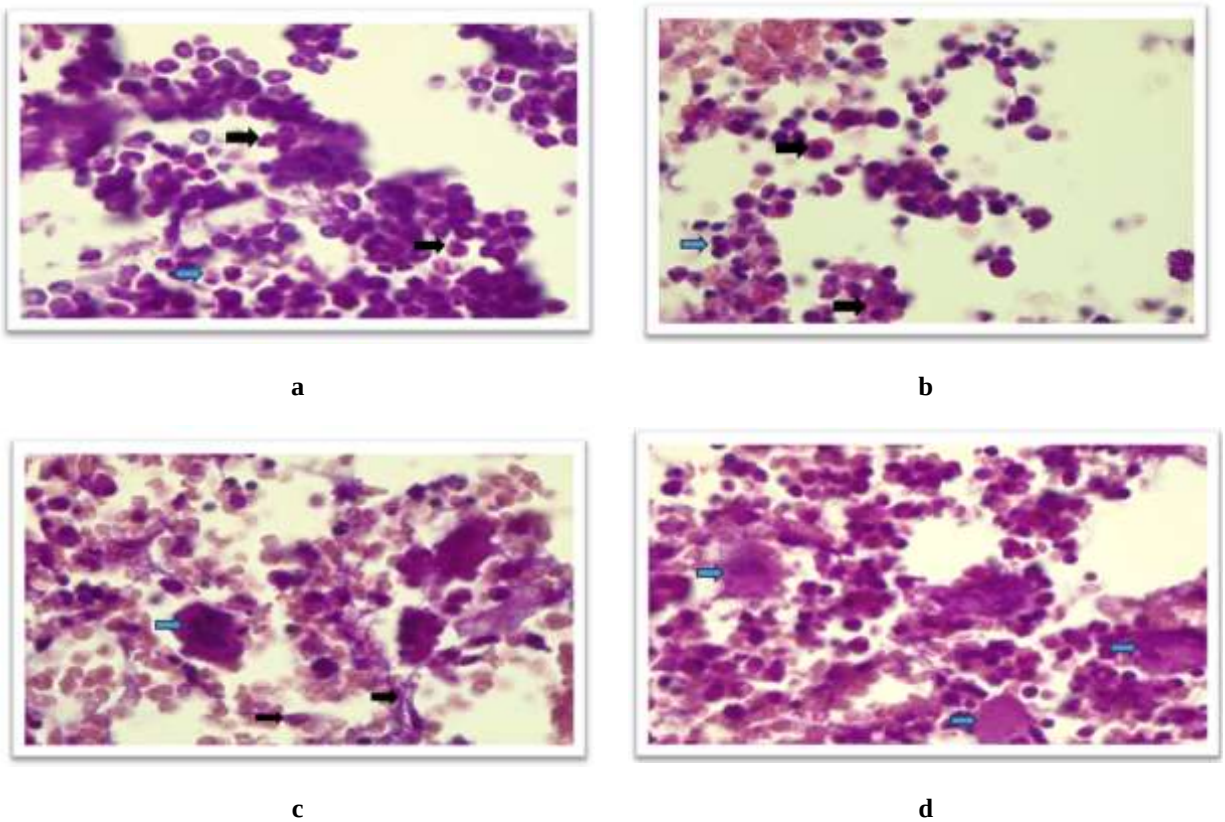


Figure 1 (a-b). Values presented as mean ± SEM, (N=7) for each group. * denotes significant elevation compared with the control group (p<0.05); # and ~ denotes significant reduction compared with the LPS group (p<0.05); + denotes the advantage of one of these two drugs.



Continued Figure 1.

Histopathological studies



a **b**

c **d**

Figure 2 (a-d): *(a)* Control: Both normal distribution and appearance of cells, like eosinophil metamyelocytes (black arrow) and Neutrophil myelocytes (blue arrow). H.& E (x40). *(b)* LPS decreased hematopoietic cells over RBCs. Some cells are hypertrophic (black arrow), while some are multinucleated (blue arrow). H.& E (x100). *(c)* DEX-LPS; Lower hematopoietic precursors and pro-inflammatory cells. The compressed parenchymal cells have big lobulated nuclei (blue arrow), unlike the prior group. Black arrows show hypertrophied trabecula; H.& E (x100). *(d)* MONT-LPS: The decreased number of pro-inflammatory cells and increase in the parenchymal tissue (blue arrow). H.& E (x100).

Discussion

In both health and illness, mesenchymal stromal cells (MSCs) in bone marrow strictly regulate the homeostasis of hematopoietic stem cells (HSCs) [35]. Many investigations have shown that LPS stimulates the immune system and causes a rapid and strong inflammatory response in experimental animals [36,37]. After a single dose of intraperitoneal LPS, MDA, a measure of lipid peroxidation, was significantly raised, indicating that LPS at this dose stimulates oxidative stress (OS) by liberating free radicals that can target membrane phospholipids or PUFAs [38]. LPS recognized by TLR-4 receptors and activates pro-inflammatory proteins such as NF- κB, AP-1, and IRF-3 through two signaling pathways (MYD-88 and TIRAP-IFN-β). The translocation of these factors to the nucleus increases the transcription and gene expression of inflammatory cytokines like TNF-α and IL-6, leading to MCP-1 production and phagocytic cell recruitment; This leads to more ROS production, which in turn, activates pro-inflammatory factors like NF-κB and AP-1, resulting in a vicious cycle of tissue damage [39].

Pretreatment with dexamethasone (group III), a powerful anti-inflammatory glucocorticoid, significantly reduced MDA levels compared to the model (group II). However, it is still more than control group and lower than group IV (Table 1, Figure 1-A). Dexamethasone caused a significant MPO reduction though it did not reach the basal line values of the control group (Table 1). On the other hand, Dexamethasone inhibits NF-κB, a master transcription factor that controls cytokine synthesis, such as TNF-α and IL-6, leading to anti-inflammatory features. Dexamethasone reverses the effects of ROS on NF-κB and interrupts the cycle that produces more free radicals. Some studies revealed that dexamethasone can induce lipid peroxidation and raise MDA levels when taken by injection alone (high doses) and for a longer time [40,41]. By inhibiting phospholipase A2, dexamethasone and other corticosteroids reduce the release of arachidonic acid, one of the main PUFAs from cell membrane phospholipids [42], thus decreasing ROS precursors and substrates, lowering lipid peroxidation and MDA. It is worth noting that as a defensive measure, bone marrow MPO was significantly elevated in the LPS-model group, suggesting that neutrophils and other innate immune cells are recruited to the site(s) of injury and released this dual-role MPO to help in microbial killing [24]; besides, increased level in other non-microbial inflammatory conditions like cholelithiasis [43].

Pretreatment with montelukast (group IV) caused MDA levels to decrease significantly compared to the LPS model, but they remained higher than control and DEX-LPS groups (Table 1, Figure 1-A). This finding is in line with another previous study which showed that montelukast could decrease lipid peroxidation [44]. However, montelukast significantly reduced MPO levels compared to LPS-model group II and DEX-LPS (group III); this shows its anti-oxidant effectiveness as it normalizes MPO levels (to baseline in control) since there is no significant difference with control (p<0.05) (Table 1). As shown by previous studies, montelukast protects against acute pancreatitis by reducing neutrophil infiltration, thus reducing MPO levels and inflammation [36]; Moreover, it has protection against acute liver injury by a similar mechanism [37].

In histopathological examinations, a relatively pale slide appearance (LPS group) indicated a marked reduction in hematopoiesis and replacement with fatty tissue compared to the control group (Table 2). Further investigations like hematopoietic cell count and differential WBC count in blood are needed, but this study focused on LPS's inflammatory and oxidative effects on this tissue. The host bone marrow first combats LPS-induced infection by increasing the supply and mobilization of WBCs such as neutrophils and monocytes to the damaged site. However, the net effect may end up producing HSC depletion, hypocellularity, and cell hypertrophy in bone marrow [39]. Pretreatment with dexamethasone decreased pro-inflammatory cells, and increased fat tissue compared to the control group (Table 2) in line with other previous study said that dexamethasone increased bone marrow adiposity [45]. Pretreatment with montelukast showed a decrease in pro-inflammatory cells, with less adiposity compared with the DEX-LPS group (Table 2).

Limitations and Recommendations

In this study; we did not use multiple graded doses of dexamethasone to study their effect on MDA and MPO; Besides, the serious adverse effects of dexamethasone prevent us from using it for longer periods to study the long-term effect on both MDA and MPO. Another limitation is the difficulty with blood sample collection at different times after LPS injection (for instance after 6, 12, and 18 hours) which would aid in follow-up MDA and MPO levels.

Additional groups can be added for further work using natural antioxidants alone or in combination with montelukast (e.g. resveratrol, ascorbic acid, or tocopherol).

Conclusion

According to the results obtained from this study, montelukast could be used as a powerful anti-oxidant to restore the balance between prooxidant and anti-oxidant defense. At first, it has a smaller impact on lipid peroxidation compared with

dexamethasone despite a significant reduction compared with the LPS-model group; However, further studies are required to investigate whether with time, and owing to its excellent control on MPO, montelukast may reduce the impacts of ROS on phospholipids, thus reducing lipid peroxidation and MDA levels.

Dexamethasone can be used in low doses over a short interval to reduce lipid peroxidation but has a smaller impact on MPO compared with montelukast despite the significant reduction compared with the LPS-model group.

Conflicts of Interest

The authors declare that no conflicts of interest.

Funding

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Ethics Statements

The Scientific and Ethical Committee of the College of Pharmacy, University of Baghdad, approved the present study.

Author Contribution

Concept – Ahmed Hamed Jwaid.; Design – Ahmed Hamed Jwaid.; Supervision – Ahmed Hamed Jwaid; Resources – Rami Isam Kamal; Materials – Rami Isam Kamal; Data Collection and/or Processing – Rami Isam Kamal.; Analysis and/or Interpretation – Rami Isam Kamal.; Literature Search – Rami Isam Kamal; Writing – Rami Isam Kamal.; Critical Reviews – Ahmed Hamed Jwaid.

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دراسة مقارنة بين دواء المونتيلوكاست مع الديكساميثازون في الوقاية المحتملة من الاجهاد التأكسدي المستحث بمادة عديد السكاريد الدهني في نخاع العظم لذكور فئران ألبينو

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الخلاصة

الاجهاد التأكسدي هي حالة تنشأ عندما لاتستطيع دفاعات المضيف المضادة للأكسدة الصمود امام الهجوم الشرس من جذور الاوكسجين والنتروجين الحرة. عدم الاتزان بين محفزات الاكسدة ومضادات الاكسدة يسبب أمراض الغدد الصماء، الامراض القلبية الوعائية، الأمراض الرئوية والأمراض العصبية. خلال الاصابة بالانتان، عدم الاتزان هذا يسبب فشل الاعضاء ومنها نخاع العظم. ولهذا الغرض، تقسيم ثمانية وعشرون فأر عشوائيا الى اربعة مجموعات بواقع سبعة لكل مجموعة وكالتالي: المجموعة الاولى تم اعطائها الماء المقطر بواسطة انبوب الزق الفموي مرة يوميا و لمدة اسبوع، ثم التضحية بها في اليوم الثامن. المجموعة الثانية تم اعطائها جرعة منفردة من مادة عديد السكاريد الدهني ١٠ملغ/كغم زرقا في البيريتون، ثم التضحية بها في اليوم الثاني. المجموعة الثالثة تم اعطائها الديكساميثازون ٢,٥ ملغ/كغم، بواسطة انبوب الزق الفموي مرة يوميا ولمدة اسبوع، وبعد ساعتين من الجرعة الاخيرة ، اعطيت مادة عديد السكاريد الدهني، ثم التضحية بهم في اليوم الثامن. المجموعة الرابعة تم اعطائها المونتيلوكاست ٢٠ ملغ/كغم، بواسطة انبوب الزق الفموي مرة يوميا ولمدة اسبوع، وبعد ساعتين من الجرعة الاخيرة، اعطيت مادة عديد السكاريد الدهني، ثم التضحية بهم في اليوم الثامن. أظهرت النتائج ارتفاع مستويات المالونداي الديهايد وكذلك المايلوبيروكسيديز في المجموعة الثانية (عديد السكاريد الدهني) مقارنة مع المجموعة الأولى. وقد كشف العلاج الاستباقي بدواء الديكساميثازون(المجموعة الثالثة) والمونتيلوكاست(المجموعة الرابعة) تقليل مستويات المالونداي الديهايد والمايلوبيروكسيديز. اما نتائج الفحص النسيجي الخلوي بينت ان المونتيلوكاست قلل الخلايا الالتهابية من دون التأثيرعلى الكريات الحمراء. كاستنتاج، دواء المونتيلوكاست له تأثير واعد كمضاد اكسدة فعال وربما يكون خيارا كعلاج وقائي من النتائج الوخيمة للإجهاد التأكسدي في البشر.

الكلمات المفتاحية: ديكساميثازون، عديد السكاريد الدهني، مونتيلوكاست، الاجهاد التأكسدي، الانتان.