ORIGINAL ARTICLE

Dexamethasone and Pentoxifylline Combination Therapy in Aversion of Lipopolysaccharide Induced Hepatotoxicity in BALB/C Mice

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ABSTRACT

Objective: To evaluate the combined effect of dexamethasone, and a phosphodiesterase inhibitor, pentoxifylline, in aversion of LPS/endotoxin induced hepatotoxicity in BALB/c mice.

Study Design: An experimental study.

Place and Duration of Study: Department of Pharmacology and Therapeutics, Army Medical College, NUST, Rawalpindi over a period of 3 months (March 2015-June 2015).

Materials and Methods: Thirty animals were divided into 5 groups, each group having six animals. The animals were injected intraperitoneally with normal saline (Group 1), lipopolysaccharide(LPS) of serotype E.Coli (Group2), low dose steroid-dexamethasone after LPS (3mg/kg of body weight)(Group 3) , pentoxifylline (PTX) (75 mg/kg of body weight) (Group 4) after LPS and in the last group coadministration of dexamethasone and pentoxifylline after LPS (Group 5).The extent of liver damage was adjudged via serum alanine aminotransferases (ALT) and aspartate aminotransferase (AST) estimation along with histopathological examination of liver tissue.

Results: Lipopolysaccharide administration in animals of Group 2 resulted in marked hepatotoxicity as evident by statistically significantly escalated serum aminotransferases and pronounced inflammation on liver tissue cross section examination. Dexamethasone (Group 3). Pentoxifylline (Group 4) and combined treatment (Group 5) abated considerably serum ALT levels at 17 hours when compared to LPS group (Group 1) yielding a p value of ≤ 0.01 for each group. Serum AST levels also declined statistically significantly giving a p value of ≤ 0.01 when LPS group (Group 1) is compared to Group 3, 4 and 5 respectively. Histological examination revealed that Dexamethasone (Group 3). Pentoxifylline (Group 4) and combined treatment (Group 5) reduced inflammation and necrosis produced by LPS in Group 2. However combined treatment results were akin to individual drug therapy alteration.

Conclusion: Treatment of lipopolysaccharide (LPS/endotoxin) induced hepatotoxicity with dexamethasone, and phosphodiesterase inhibitor, pentoxifylline in LPS/endotoxin showed encouraging results in our study.

Key Words: *Dexamethasone, Endotoxin, Hepatotoxicity, Lipopolysaccharides, Pentoxifylline*.

Introduction

Human immune system where functions to protect our race from deadly infections, can also produce an exaggerated and overwhelming immune response causing systemic inflammation, tissue damage and sepsis. Sepsis and related organ failure are a global health crisis leading to high morbidity and mortality. Though difficult to determine the disease burden, almost 30 million people suffer from sepsis annually and 6 million lose their lives to this deadly disease and risk is likely highest in low and middle-income countries.[1,2] Those who do survive are left with life-changing effects, such as post-traumatic stress disorder (PTSD), chronic pain and fatigue, and organ dysfunction and/or amputations.

Initially gram-negative bacteria were the main culprit of sepsis and associated organ failure but with the more utilization of invasive procedures and increasing ratios of hospital acquired infection, gram positive bacterial infections are also common.[3]

The eventual death in sepsis results from organ

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failure and liver injury plays a pivotal role in commencement and augmentation of multiple organ failure. Liver via hepatocytes (HCs), Küpffer cells (KCs), and sinusoidal endothelial cells (SECs plays a crucial part in endotoxin /bacteria scavenging, detoxification, and synthesizing proteins for metabolic, immune, and coagulation functions. The pathological part of gram-negative bacterial cell wall called lipopolysaccharide (LPS), through its interaction with Toll like receptors on Kupffer cells, elicit production of inflammatory cytokines including TNF-alpha, various interleukins (ILs), reactive oxygen-nitrogen species, lipid mediators like thromboxane A2, and proteases; all producing hepatocytes dysfunction in counteraction to LPS.[4,7]

Studies document that low dose steroid therapy (300mg/day hydrocortisone or equivalent) expedite shock reversal.[8,10] It amends hemodynamic instability through up regulation of catecholamine receptors which were desensitized by high cortisol levels and decline production of nitrous oxide.[10,11] Also reported that it markedly decreases inflammatory mediators TNF-alpha, IL-10, IL-6, IL-8, C-reactive proteins, decline release of hydrogen peroxide from neutrophils, improves endothelial dysfunction, ameliorates coagulation disorder and reduces the severity of organ failure including hepatotoxicity.[10,5]

Pentoxifylline (PTX) is an all-around and wide range phosphodiesterase inhibitor and adenosine receptor agonist/antagonist. Studies have demonstrated that pentoxifylline beneficial effects are attributed to reduction of LPS induced production of TNF-α followed by decline in IL-1β, IL-12, IL-8 and inducible nitric oxide synthase production with up-gradation of anti-inflammatory circle through IL-10. Pentoxifylline has demonstrated to reduce expression of ICAM-1 adhesion molecules on endothelial cells, diminished neutrophils polarization, chemotaxis and degranulation, abated cytotoxicity of natural killer cells, contracted T-lymphocytes cell proliferation, adhesion and trans endothelial migration and reduction of plasma concentration of markers of apoptosis, Fas/Apo-1.[16]

Till date the treatment of sepsis and associated hepatotoxicity include specific antibiotics, fluid therapy, and use of supportive care including steroids and vasopressors. Invention of newer treatment modalities and reevaluation of previous strategies is the dire need of time to reduce disease burden globally.

This study was aimed to discover the combined dexamethasone and pentoxifylline therapy efficiency and compare with individual agent therapy in treatment of lipopolysaccharide induced hepatotoxicity in white albino mice.

Materials and Methods

It was an experimental study in which majority of the extraneous factors like age, diet, gender, environment, health status, lightening and housing conditions were accounted for.[17] This study was carried out in the Department of Pharmacology and Therapeutics, Army Medical College, NUST, Rawalpindi over a period of 3 months from March 2015 to June 2015. All experimental protocols described in this study complied with "Centre of Research in Experimental and applied Medicine (CREAM)" Army Medical College ethics review committee for animal experimentation.

Thirty BAL/B mice weighing 40-50 grams, aged 8 to 12 weeks were used throughout the study. All animals were placed in traditional wire topped, square shaped mouse cages at 20-22°C with humidity maintained at 40-70%. Contamination free fresh water and nutritionally adequate rodent pellet diet (containing 4-7% fat and 11-15% protein) was provided.[17]

Lipopolysaccharides (LPS) from Escherichia Coli O111:B4

LPS, provided by Sigma chemicals, USA had been extracted by phenol method containing 16 % RNA and 1% protein. We selected 10mg/kg of body weight, intraperitoneally as our study dose.[18] Dexamethasone was purchased locally and we selected 3mg/kg of body weight, intraperitoneally as our study dose.[15,18] Pentoxifylline was purchased from Sigma Aldrich chemical USA. After a pilot study, 75 mg/kg of body weight, intraperitoneally was well tolerated by animals and hence was taken as our study dose. Other reagents used in study includes Phosphate buffered normal saline for preparation of lipopolysaccharide solution, absolute ethanol, and normal saline for preparation of melatonin and 10% formaldehyde for preserving tissues.

Again, a pilot study was carried out to determine the hepatotoxic dose of LPS in BALB/B mice. A dose of 10mg/kg of body weight, intraperitoneally and time

interval of 17 hours between LPS administration and terminal sampling of mice proved effectual for reproduction of hepatotoxic model.

Animals were segregated into control group receiving intraperitoneal normal saline (Group 1), in toxic group receiving 10mg/kg of body weight, intraperitoneally LPS (Group 2) and into dexamethasone treatment group receiving 3mg/kg of body weight, intraperitoneally two hours after LPS administration (Group 3). In Group 4, due to rapid elimination kinetics of pentoxifylline, it was administered twice, first 2 hours after LPS injection at a dose 75mg/kg of body weight and secondly seven hours after LPS administration at the same dose. Animals of group 5 were co-treated with dexamethasone and two doses of Pentoxifylline at mentioned protocol, two hours after LPS injection.

The first blood sample at the start of experiment (zero hours) was taken from lateral tail vein of mouse as per protocols approved by Institutional Animal Care and Use Committee (IACUC).[19] Drop jar method utilizing 20% v/v isoflurane in propylene glycol solution-soaked cotton gauze in bell jar was selected for terminal anesthesia followed by cardiac puncture sampling through closed ventral approach and midline laparotomy for liver removal. Tissue was immediately fixed in 10 % formaldehyde and blood samples were stored at 4°C for latter chemical analysis.

Septicemia led to variable histopathological changes in liver as reported by several studies, we decided to use Ishak Modified Histological Activity Index as scoring system.[20] Score of one to four ranked as moderate inflammation and severe inflammatory changes due to sepsis produced score of fifteen to eighteen. Also, serum elevations in ALT and AST levels were measured for the determination of hepatic injury.

Data was entered in statistical package for social sciences (SPSS) version 20. The results of the serum analysis were expressed as Means + Standard Error of Means. The statistical significance of differences between means were analyzed with one way analysis of variance (ANOVA) followed by Post-hoc tukey test. Statistical difference between serum marker at initial and final hours were found using Paired T-test. Independent / unpaired T-test was utilized to access difference of serum markers at 17 hours on LPS group with another. The result of histopathology was analyzed using the "Chi-square test". All values were considered statistically significant if "p value" was equal or less than 0.05.

Results

Serum ALT and AST levels did not rise statistically significantly after administration of normal saline in mice of Group 1 (Control group) (Table I).

Animal of Group 2 receiving intraperitoneal LPS were prostrated and worn out during seventeen hours of experimentation with serum ALT and AST levels rising to much higher values, a statistically significant difference when compared to levels at zero hour (Table I).

Serum ALT and AST levels did not increase significantly at 17 hours blood sampling of mice in Group 3 (dexamethasone after LPS) and Group 4(pentoxifylline after LPS) (Table I). Similar results were seen with co-administration of dexamethasone and pentoxifylline in animals of Group 5. Serum ALT levels again failed to rise at 17 hours yielding an insignificant p value (0.316). Same was the case with serum AST yielding a p value of 0.142. (Table I).

Table I: Comparison of Means and ±SEM of Serum ALT and AST levels at Zero and 17 hours of each Group

Groups	Group1 (Control)	Group 2 (LPS)	Group 3(DEXA)	Group 4(PTX)	Group 5(DEXA +PTX)
Serum ALT at 0 hour	109.5±3.09	106.5 ±3.09	104.5 ± 2.51	97.83±1.13	101.3± 4.1
Serum ALT at 17 hours	106.6±2.23	345.16±76.5	114 ±16.5	90.67± 8.4	96.5± 5.1
P value	0.276	≤0.01	0.554	0.369	0.316
Serum AST at 0 hour	90.50±4.82	90.50 ±11.8	98.33± 1.9	100.33± 2.7	99.50± 6.83
Serum AST at 17 hours	93.16±5.06	343.16±18.4	130.83±17.7	127.16±14.9	127.67±16.2
P value	0.137	≤0.01	0.118	0.147	0.142

P value ≤ 0.05 is Considered Significant.

ANOVA was run to analyze the effect of our treatment on serum ALT and AST levels (Table II &III). There was a significant difference between groups in serum ALT and AST levels at 17-hour terminal blood sampling. A post hoc comparison was carried out using Tukey HSD test that showed that mean serum ALT levels (345.2 ±76.5 IU/L) at 17 hours of Group 2 (LPS) were significantly different from Group 3, Group 4, and Group 5 (Table II &III). However, our result indicated that dexamethasone and pentoxifylline combined in Group 5 treatment is no different from individual drug treatment in Group 3 and 4 respectively (Table II &III).

Table II: ANOVA Comparisons of Mean Serum ALT Levels (IU/L) at 17 Hours of Each Group

Groups	Mean ALT(IU/L)	SEM		Tukey's HSD Comparisons The mean difference is significant at the 0.05 level			
			Group 1 (Control)	Group 2 (LPS)	Group 3 (DEXA)	Group 4 (PTX)	Group 5 (DEXA+PTX)
Group 1 (Control)	106.7	±2.2		<0.001	1.00	1.00	1.00
Group 2 (LPS)	345.16	±76.5	<0.001		<0.001	<0.001	<0.001
Group 3 (DEXA)	114	±16.5	0.99	<0.001		1.0	1.0
Group 4 (PTX)	90.67	±8.4	1.0	<0.001	1.0		1.0
Group 5 (DEXA +PXT)	96.5	±5.1	1.0	<0.001	1.0	1.0	

Table III: ANOVA Comparisons of Mean Serum AST Levels (IU/L) at 17 Hours of Each Group

Groups	Mean AST(IU/L)	SEM	Tukey's HSD Comparisons The mean difference is significant at the 0.05 level				
			Group 1 (control)	Group2 (LPS)	Group 3 (DEXA)	Group 4 (PTX)	Group 5 (DEXA +PTX)
Group 1 (control)	93.1	±5.0		<0.001	0.715	0.800	0.789
Group 2 (LPS)	343.2	±18.5	<0.001		<0.001	<0.001	<0.001
Group 3 (DEXA)	130.8	±17.7	0.715	<0.001		1.00	1.00
Group 4 (PTX)	127.2	±14.9	0.800	<0.001	1.0		1.0
Group 5 (DEXA +PTX)	127.2	±16.4	0.789	<0.001	1.0	1.0	

Histopathological Examination: Liver slides were observed through light microscope at 10X, 20X and 40X magnification and were assorted according to criteria described (ISHAK/Knoddels criteria). Histopathological analysis of sections of liver of six animals of Group 1 depicted the normal lobular organization of mouse liver that is hepatic triad and hepatocytes cord radiating from central venule and were graded as normal according to Ishak's criteria (Figure 1). In Group 2(LPS), marked inflammatory changes consisting of cellular infiltrates, loss of cellular organizations and periportal inflammation were evident (Figure 1). Whereas cross-section examination of liver slides of Group 3(dexamethasone after LPS), Group 4(pentoxifylline after LPS) and Group 5 (dexamethasone + pentoxifylline after LPS) exhibited negligible inflammatory cells aggregation in and around few portal areas (Figure 1). They were graded as minimal inflammation in liver. As both variables are categorical and sample size is large, the Chi-Square test of association was employed to ascertain the statistical worth between the groups and histological grading. Most eloquent change was when Group 2 (LPS Group) was compared to Control group (Group 1) with p value ≤ 0. 007.Comparison of Group 2 (LPS Group) with Group 3 (dexamethasone after LPS), Group 4 (pentoxifylline after LPS) Group 4 (dexamethasone + pentoxifylline after LPS) all yielded a statistically compelling difference as p value of ≤ 0.05 in each group.

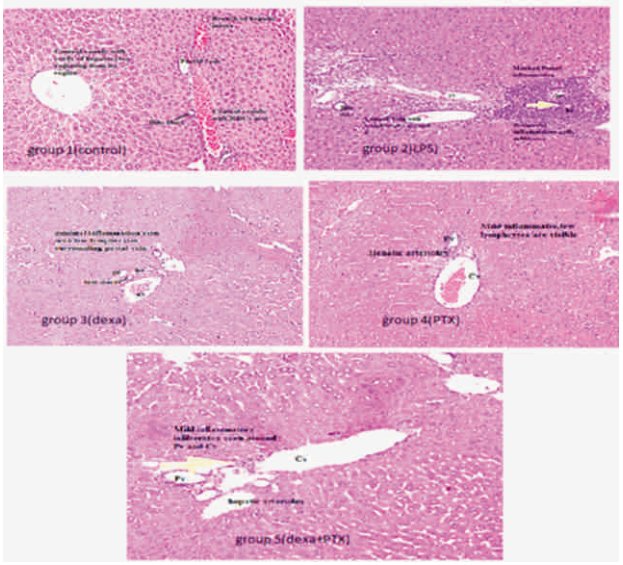

Fig 1: Mouse Liver Histology at 20X of Group 1,2,3 and 4 Clockwise. Pv-Portal Vein, Cv Centarl Vein and Ha-Hepatic Arteriole

Discussion

Considering the immense immune mediated reaction in sepsis induced hepatic failure, this study was designed to evaluate the protective effects of dexamethasone and pentoxifylline as a combination therapy. We have shown in our study that dexamethasone and pentoxifylline alone and as a combination therapy offers protection against LPS induced hepatic dysfunction. Both the agents significantly abated the LPS induced spike in serum ALT and AST levels. The marked inflammation seen on liver tissue histology was decreased to minimal to moderate inflammation by dexamethasone and pentoxifylline alone and in combination. Dexamethasone hepatoprotective role in our findings is in coherent with other studies. Wang et al in 2009 certified that dexamethasone hundred percent protected wild-type mice injected with high

dose of LPS (20mg/kg of body weight) from lethality.[21] Aytac in 2014 also demonstrated that same dose of dexamethasone improved survival and lessened liver injury in septic mice.[10] Our second experimental agent ,Pentoxifylline through suppression of TNF-α production and PDE inhibition, has been investigated in many inflammatory disorders including sepsis and retains favorable results like our study.[22,23]

Although evidence-based treatment protocols have been implemented across the world, sepsis with organ failure is still a health hazard in developing countries like Pakistan.

Lipopolysaccharide (LPS) activates host innate response through lipopolysaccharide binding protein (LBP) and CD14 receptors resulting in activation of kinases cascade with phosphorylation of series of adaptor proteins. In liver, TNF-alpha and IL-1 are antecedent inflammatory cytokines followed by production of IL-6, IL-8, IL-10, adhesion molecules and NO synthase. There's also activation of endothelial cells promoting fibrin deposition in sinusoids. [7] As a result there is hepatocytes dysfunction in counteraction to LPS.

Dexamethasone has been shown to markedly decrease the inflammatory mediators, decline release of hydrogen peroxide from neutrophils, improves endothelial dysfunction, ameliorates coagulation disorder, and reduces the severity of organ failure including hepatotoxicity in septic patients. [10-15] Several mechanisms have been explained for this hepato-protective role in LPS induced septicemia. Studies have shown that dexamethasone induces production of anti-inflammatory proteins (annexin-1, MAPK phosphatase and inhibitors of NF-kβ).[10-15] Studies have also documented that direct and indirect organization of glucocorticoid-cytoplasmic glucocorticoid receptor with pro-inflammatory gene transcription factor like Activator protein 1 (AP-1) and NF-kβ inhibits their nuclear translocation and transactivation function. [10-15]Our study also support this anti-inflammatory role of dexamethasone in animals of Group 3 where in mice, injected with physiological and clinically applicable dose of 3mg/kg of body weight of dexamethasone after LPS administration, were protected from hepatotoxicity.

Our study second experimental agent was Pentoxifylline (PTX). It is a broad-spectrum phosphodiesterase inhibitor and adenosine receptor agonist/antagonist that has been utilized clinically for hemorheological disease. However, several studies have also proved its beneficial role through heterogeneous pathways for treatment of sepsis. Pentoxifylline (PTX) increases intracellular concentration of cAMP and cGMP in inflammatory cells line through inhibition of PDE4 and PDE7. This through activation of protein kinase A (PKA) and cAMP response element binding protein (CREB) down regulates NF-κB activity and diminishes TNF-alpha production.[16,22]These results support our study results wherein pentoxifylline lessened degree of hepatic dysfunction as evident by reduced serum ALT and AST levels and minimal inflammation on histological examination of liver cross sections.

We have adjudged the role of individual drugs in aversion of LPS induced liver injury in our previous studies, however we were intrigued by the question whether these two drugs perform additively or not. For this purpose, we attested our animals of Group 5 with Dexamethasone 3mg/kg intraperitoneally along with two doses of pentoxifylline (75mg/kg i.p.) two hours after LPS administration. The combination did restore serum amino transferases levels significantly (ALT p≤ 0.01 & AST p value≤ 0.01) but essentially like individual dexamethasone and pentoxifylline effect in Group.3 and Group 4 respectively. Hepatic inflammatory and necrotic changes annulment was also statistically significant (p≤0.05).

Study results of Saez-Llorens and fellows substantiated our findings. They revealed no synergism between dexamethasone and pentoxifylline in declination of meningeal inflammation produced by intra-cisternal injection of endotoxin.[23] Hand and friends demonstrated that concomitant dexamethasone and pentoxifylline inhibited LPS induced TNF synthesis to a greater level than either agent alone by acting on different points in endotoxin evoked signaling pathway.[24] Due to unavailability of TNF-α levels measurement in our study we cannot firmly say their findings are non-compatible to ours, but we are undoubtedly of the view that combination therapy did not diminish TNF-α downstream inflammation symbiotically.

Future work should be carried out on combination

regimens via methodology alteration.

Conclusion

Dexamethasone and pentoxifylline both showed promising result in our study and significantly ameliorated lipopolysaccharide induced hepatotoxicity and hence. However, combination therapy has no superior role in treatment of LPS/endotoxin induced hepatotoxicity when compared to individual agent alone.

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