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Dexmedetomidine Alleviates Rat Liver Histopathology during Experimental Sepsis

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ABSTRACT

Introduction: The Food & Drug administration has approved a new sedative dexmedetomidine, an imidazole compound with high affinity for adrenoceptors (alpha 2). for use in critical care units. Its other pharmacological effects include anxiolytic and lung ischemia reducing abilities. The liver being a vital organ for drug biotransformation and general body function may bear the brunt of dexmeditomidine effects. Prolonged use of dexmedetomidine in deeply sedated ccu patients who frequently suffer from sepsis requires scientific study of dexmedetomidine's hepatic effects under pre clinical simulated circumstances before human studies can be conducted.

Aims and Objectives: The purpose of this study is to determine the histopathological changes of dexmedetomidine during septicemia in the preclinical rat model.

Place and Duration of study: Study was performed in the Animal House of Post Graduate Medical Institute, Lahore for 15 days.

Material and Methods: Our study agreement was analyzed and accepted by Ethical Committee at Post Graduate medical Institute, Lahore. Female rats weighing 200-250 grams for 7 weeks. One week before experiment animals were adapted in the lab maintained at 22 ± 2 C in a persistent 12 hrs. light/ dark cycle. Data was entered and analyzed using SPSS version 25. P-Value of < 0.05 was considered statistically significant.

Results: Control group did not show any change. Three mortalities were observed in toxic groups. Total scoring of pathological alterations in liver was done. Tissue scoring of control group was 0.4 ± 0.52. In septic group it was 4.5 ± 0.9 & 1.5 ± 0.80 in the dexmedetomidine groups. The mean of total scoring of variations of tissues showed a statistically significant difference.

Conclusion: It's concluded that dexmedetomidine induced significant ameliorative changes in histology of rat liver during sepsis.

Key Words: Increasing trend, gestational diabetes, pregnant, females.

INTRODUCTION

Food & Drug Administration has approved a new antidepressant dexmedetomidine for use in critical care unit. It is an imidazole compound with high affinity for adrenoceptors (alpha 2)[1]. Other qualities include antianxiety and less respiratory difficulties. Recent studies have shown it to be helpful in sedating pediatric patients in hospitals[2]. Dexmedetomidine has shown to be helpful in decreasing the duration of dizziness in different patients[4]. Different experimental studies revealed that dexmedetomidine has a defensive role in the prevention of oxidative toxicity[5]. Other studies have shown that dexmedetomidine is protective in reperfusion injury due to ischemia Experimental studies also revealed the beneficial effects of dexmedetomidine on pulmonary functions[7].

In different studies, dexmedetomidine has been shown to inhibit organ damage i.e. liver & kidney and inflammatory response. The beneficial effects of dexmedetomidine are better sedation & hemodynamic stabilization[6].

The leading cause of death in hospitals is sepsis which is a disorder resulting from the response of host to infectious substances[9]. Patients admitted in critical care units need prolonged sedation and require agents like dexmedetomidine. The purpose of this study is to explain the histopathological changes of dexmedetomidine on liver during septicemia in rats.

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MATERIAL AND METHODS

Study was performed in the Animal House of Post Graduate Medical Institute, Lahore for 15 days. Our study agreement was analyzed and accepted by Ethical Committee of the Post Graduate Medical Institute, Lahore IRB Number (UHS /Education / 135-12 /85). Female rats weighing 200 - 250 grams for 7 weeks. One week before experiment animals were adapted in the lab and maintained at 22 ± 2 C in a persistent 12 hrs. Light/ Dark cycle. Rats were kept in iron cages and fed with regular diet.

Grouping of animals:

Animals were randomly divided into three groups

1. Toxic group (n:8): Toxemia was introduced by injection of E.coli administered IV at 12mg/kg over 2 min.
2. Toxic group with dexmedetomidine (n:8): Toxicities were induced and dexmedetomidine was given IV at 15mg/ kg over 4 min
3. Control group (n:8): In this group animals were treated with 0.8% saline only

Histological Examination:

After six hours of toxin infusion the rats were administered 250 mg /kg of pentothal sodium to anaesthetize, sacrificed and a median laparotomy was conducted to separate the liver. Livers were resected and emerged in 12% formaldehyde for 20 hours and fixed into paraffin after 14 hours of processing with alcohol treatment. Six micrometer thick sections were separated from paraffin blocks and stained. Pathologist examined each slide under light microscope. Congestion of central veins and enlargement of hepatic sinusoids and swelling of portal tracts were observed and grading was done from 1- 4.

Grade 1: (Fig-1): showing no change,

Grade 2: (Fig-2): showing minimal changes,

Grade 3: (Fig-3): presenting medium changes and

Grade 4: (Fig-4): with extreme effects

Collection of all grades was considered as total score ranging from 1-8.

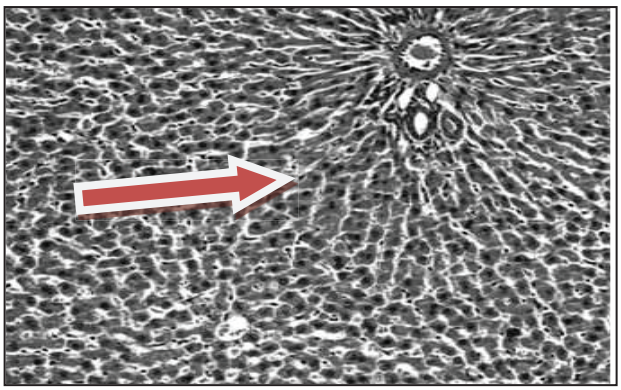

Fig-1: No Change

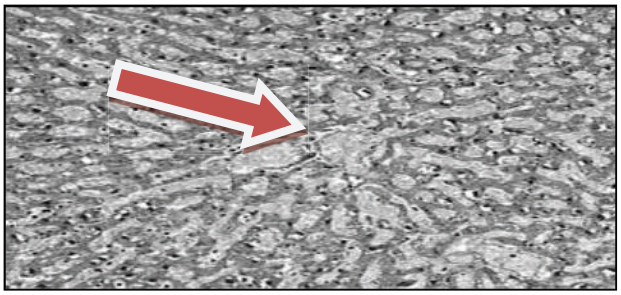

Fig-2: Mild Change

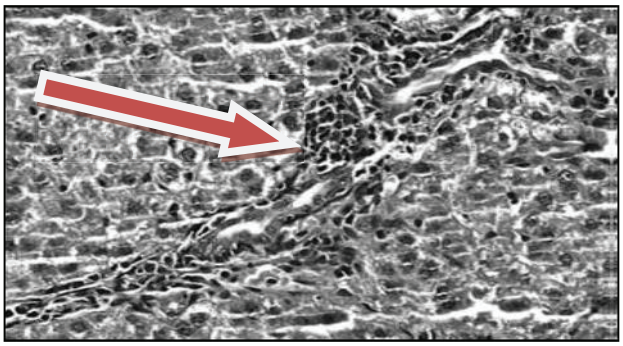

Fig-3: Moderate change

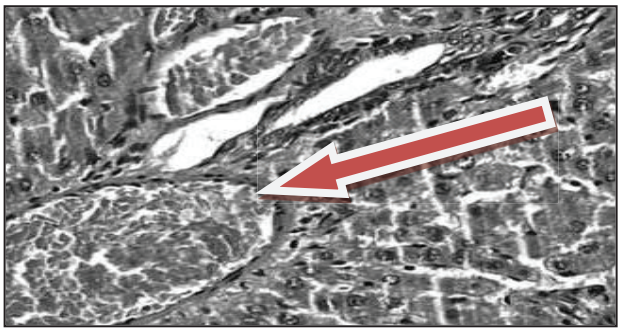

Fig-4: Severe Changes

Three rats showed engorgement of central veins, others showed congestion of medium degree in toxic group. Five rats showed mild engorgement of central vein in dexmedetomidine group. Statistically significant difference was appreciated in two groups with p value < 0.001. Eight rats of dexmedetomidine presented with mild venous engorgement.

Mild inflammation was seen in portal system of livers of septic group while only two moderate portal system swellings were observed in dexmedetomidine group. Statistically significant difference was found between two groups p-value <0.002.

Statistical Analysis:

SPSS version 25 was used for statistical analysis. To compare the difference between groups Kruskal Wallis test was performed and Neman test was used when a significant difference was obtained. Statistically significant P value is < 0.05.

RESULTS

Control group did not show any change. Three mortalities were observed in toxic groups. Total scoring of pathological alterations in liver was done. Tissue scoring of control group was 0.03 ± 0.52. In septic group it was 4.5 ± 0.02 & in dexmedetomidine group it was 1.6 ± 0.72. The mean of total scoring variations of tissues showed a statistically significant difference in groups (p-value<0.001). (Table 1)

Tissue effects	Control (n=8)	Dexmedetomidine (n=8)	Sepsis (n=8)	P-value
Congestion of central vein	0.25± 0.40	0.6± 0.53	3.4± 0.52	<0.002
Sinusoidal obstruction	0.02± 0.43	0.2± 0.42	1.2± 0.42	<0.001
Swelling of portal tracts	0.01± 0.02	0.8± 0.52	1.8± 0.53	<0.002
Total	**0.03± 0.52**	**1.6± 0.72**	**4.5± 0.02**	**<0.001**

Table-1: Rat liver tissue variables.

DISCUSSION

This study was designed to illustrate the protective effect of dexmedetomidine on liver of toxic animals. It was assumed that dexmedetomidine reduces liver destruction related to toxicity and shock. Toxemia is a leading cause of death in critical care units which is treated on urgent basis. Present study was designed to demonstrate the beneficial effects of dexmedetomidine on liver tissue destruction in toxic groups. It was observed that dexmedetomidine lowers congestion of central veins, similar changes were observed in another study where dexmedetomidine reduced liver toxicity caused by lipopolysaccharides[10]. Another study revealed that tissue ischemia of liver tissue caused by hypoxia is less with dexmedetomidine[11].

It was also observed that dexmedetomidine treated group had less inflammation & congestion of hepatic sinusoids. Another study demonstrated that dexmedetomidine exhibits anti-inflammatory & antioxidant properties & hepatoprotective effect in different cases of hepatic jaundice[12].

Dexmedetomidine has shown to be highly effective in treating liver toxicity caused by infection. This study revealed that dexmedetomidine is highly recommended for treating experimental liver toxicity caused by infection.

CONCLUSION

Our study has shown the protective effect of dexmedetomidine in liver destruction due to toxicity in the rat model.

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