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COMPARATIVE STUDY OF LIVER HISTOPATHOLOGY AND TRANSAMINASE LEVELS IN DIABETIC WISTAR RATS INDUCED BY ALLOXAN AND STREPTOZOTOCIN

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ABSTRACT

Background: Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose levels. Experimental models using male Wistar rats (Rattus norvegicus) induced with alloxan (ALX) or streptozotocin (STZ) are widely applied to explore therapeutic strategies. However, several studies have reported that ALX has greater limitations compared with STZ. **Objective:** To analyze the differential effects of ALX and STZ as diabetogenic inducers in Wistar rats based on liver histopathology, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) levels. **Methods:** A post-test only control group design with simple randomization was employed. Forty-two male Wistar rats weighing ≥200 g were assigned into seven treatment groups. Independent variables included ALX and STZ at graded doses, while dependent variables were liver histopathology, SGOT, and SGPT. Histopathology was assessed using the Manja Roenigk scoring system, and enzyme levels were measured by enzymatic methods. **Results:** Significant differences were observed between ALX and STZ in liver histopathology ($p<0.001$) and SGPT levels ($p=0.001$), but not in SGOT ($p=0.199$). Histopathological findings between ALX- and STZ-induced groups were relatively comparable at equivalent doses. In contrast, SGOT and SGPT results indicated that ALX may induce resistance. **Conclusion:** ALX and STZ caused comparable hepatic damage, but STZ exhibited more stable blood biomarker profiles.

BACKGROUND

Diabetes mellitus (DM) remains a major global health problem and is widely known as a "silent killer" because it often goes undetected until severe complications arise[1,2]. DM is a chronic non-communicable disease (CNCD) of multifactorial etiology resulting from insulin insufficiency, clinically defined by random blood glucose (RBG) ≥200 mg/dL and fasting blood glucose (FBG) ≥126 mg/dL[3-5]. This condition leads to disturbances in glucose metabolism, whereby the liver, serving as the body's glucostat, undergoes microscopic structural damage and significant dysfunction, as indicated by elevated hepatic enzyme profiles such as SGOT and SGPT [6,7].

To establish effective therapeutic strategies, a series of *in vivo* studies has been conducted using experimental animals such as male Wistar rats (*Rattus norvegicus*) that are modified to mimic human DM conditions[8]. Induction with chemical agents, namely alloxan (ALX) and streptozotocin (STZ), is a commonly employed non-genetic method. ALX induces the formation of radical anions, causing pancreatic beta-cell fragmentation and a consequent reduction in insulin levels[9,10]. In contrast, STZ exhibits selective cytotoxicity toward beta-cells due to its glucose moiety, leading to necrosis and subsequent hyperglycemia[11,12].

Sub-meta-analyses over the past one and a half decades have revealed that ALX is less stable as a diabetogenic agent because of its narrow effective

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dose range, which predisposes to nephrotoxicity, hepatotoxicity, and even resistance in experimental animals[9,10]. By comparison, STZ is considered superior because of its relatively longer half-life and lower susceptibility to oxidation[13,14]. Nevertheless, its potential hepatotoxic effects may act as confounding variables, since hepatic manifestations differ between DM-related complications (e.g., fibrosis) and direct chemical hepatotoxicity[7,15]. Therefore, this study is important to conduct in order to analyze the differential effects of ALX and STZ as diabetogenic inducers in Wistar rats based on liver histopathology, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) levels.

METHODS

Study Design

This study employed a true experimental approach with a *Post-Test Only Control Group Design*. The inclusion criteria were healthy male Wistar rats (*Rattus norvegicus*), aged 3–4 months, weighing ≥200g, and without anatomical abnormalities. Exclusion criteria included the presence of anatomical abnormalities or signs of illness such as inactivity, piloerection, and soft stools. Samples were selected using simple random sampling and divided into seven groups, each consisting of six rats.

Experimental Procedure

All animals were acclimatized for seven days at the Experimental Animal Laboratory, Faculty of Medicine, Diponegoro University. A total of 42 rats were then assigned to one control group (K) receiving only standard feed and water *ad libitum*, and six experimental groups with different treatments. Groups P1, P2, and P3 were induced with alloxan (ALX) at doses of 120 mg/kgBW, 150 mg/kgBW, and 180 mg/kgBW, respectively. Groups P4, P5, and P6 were induced with streptozotocin (STZ) at doses of 20 mg/kgBW, 40 mg/kgBW, and 60 mg/kgBW, respectively. On day 15, blood samples were collected from the retro-orbital venous sinus of surviving rats for SGOT and SGPT analysis using enzymatic methods. Subsequently, termination was performed, and liver tissues were harvested for histopathological examination.

Biochemical Analysis (SGOT and SGPT)

Serum SGOT and SGPT levels were measured using the kinetic enzymatic method according to the guidelines of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

Histopathological Examination

Liver histopathology was assessed using the Manja Roenigk classification. Observations were made at 400× magnification under a light microscope across five fields (four corners and the center) in the centrilobular zone (zone 3). Each field was divided into four quadrants, and five hepatocytes per quadrant were randomly selected, yielding 20 hepatocytes per field and a total of 100 hepatocytes per specimen. Each hepatocyte was scored as follows: 1 = normal, 2 = parenchymatous degeneration, 3 = hydropic degeneration, and 4 = necrosis. The final score was calculated as (∑ normal × 1) + (∑ parenchymatous degeneration × 2) + (∑ hydropic degeneration × 3) + (∑ necrosis × 4), then averaged based on the total number of hepatocytes evaluated.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics Version 23. Normality was tested using the Shapiro–Wilk test. If normally distributed, data were analyzed using One-Way ANOVA followed by *Post Hoc* tests. If not normally distributed, the Kruskal–Wallis test and Mann–Whitney test were used to determine significant differences.

RESULTS

Liver Histopathology Score

The evaluation of liver histopathology using the Manja Roenigk classification demonstrated progressive hepatocellular damage across treatment groups compared to the control (Table 1). The control group (K) exhibited the lowest median score of 1.00 (1.00–1.01), indicating normal hepatocytes. In contrast, groups induced with alloxan (P1–P3) and streptozotocin (P4–P6) showed higher histopathological scores in a dose-dependent manner. The highest degree of hepatocellular alteration was observed in group P3 (ALX 180 mg/kgBW) with a median score of 1.82 (1.54–1.96), and group P6 (STZ 60 mg/kgBW) with a median score of 1.79 (1.72–1.80).

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Table 1. Median liver histopathology scores of Wistar rats based on the Manja Roenigk classification

Group	Score (Range)
K	1,00 (1,00 – 1,01)
P1	1,34 (1,09 – 1,54)
P2	1,53 (1,35 – 1,55)
P3	1,82 (1,54 – 1,96)
P4	1,34 (1,13 – 1,48)
P5	1,59 (1,27 – 1,68)
P6	1,79 (1,72 – 1,80)

SGOT and SGPT Levels

The results of serum biochemical analysis are summarized in Table 2.

Table 2. Median SGOT and SGPT levels of Wistar rats

Group	SGOT (U/L) Median (Range)	SGPT (U/L) Median (Range)
K	112,32 (104,61 – 160,02)	75,15 (70,41 – 89,48)
P1	118,75 (69,30 – 161,30)	47,40 (37,80 – 70,30)
P2	107,00 (100,10 – 257,32)	46,80 (44,10 – 77,07)
P3	104,10 (65,90 – 123,88)	60,85 (52,90 – 69,28)
P4	119,45 (100,50 – 149,20)	54,50 (42,20 – 70,20)
P5	159,00 (91,30 – 313,40)	87,30 (60,00 – 168,40)
P6	185,60 (124,10 – 221,90)	136,50 (87,90 – 146,30)

SGOT levels showed no significant differences between groups, although an upward trend was noted in the higher-dose STZ group (P6: 185.60 U/L, 124.10–221.90) compared to the control (K: 112.32 U/L, 104.61–160.02). In contrast, SGPT levels exhibited more pronounced changes. The control group presented a median SGPT of 75.15 U/L (70.41–89.48), whereas the highest levels were recorded in the P6 group (136.50 U/L, 87.90–146.30). These findings suggest that STZ at higher doses induced a greater elevation of SGPT compared to ALX, indicating potential differences in hepatic enzyme response to diabetogenic agents.

DISCUSSION

Differences in Liver Histopathology Scores

The liver histopathological features due to the toxic effects of alloxan (ALX) and streptozotocin (STZ) were evaluated using the Manja Roenigk scoring system. A higher average score in a tissue specimen indicated more severe damage. Statistical analysis showed a significant difference ($p < 0.001$) among the treatment groups.

The control group (K) demonstrated a significant difference compared to all treatment groups (P1, P2, P3, P4, P5, P6). This finding confirms that the administration of diabetogenic agents, both ALX and STZ, affected the microscopic condition of hepatocytes due to their hepatotoxic properties[18-20]. The treatment group P3, induced with the highest dose of ALX (180 mg/kgBW; score 1.82), exhibited the most severe damage, with a considerable number of necrotic cells. ALX induces diabetes mellitus by selectively destroying pancreatic beta cells. However, observations in several experimental animals indicated that its effects could extend systemically, causing hepatotoxicity[21,22]. This diabetogenic agent disrupts regular cellular metabolic pathways, including inactivation of specific enzymes, leading to liver damage and even necrosis[8,22]. These findings indicate that higher doses of ALX result in more severe hepatocellular injury.

A similar condition was observed with STZ administration, where the degree of hepatic damage increased in line with the dose: group P4 at 20 mg/kgBW (score 1.34), group P5 at 40 mg/kgBW (score 1.59), and group P6 at 60 mg/kgBW (score 1.79). This shows that STZ also possesses dose-dependent hepatotoxic effects. Nevertheless, when compared with ALX-induced groups, the severity of liver damage in the highest STZ dose (P6) tended to be lower than in the highest ALX dose (P3), although the difference was not statistically significant ($p = 0.117$). This may be attributed to the selective hepatotoxic effect of ALX, which produces more pronounced hepatic injury[13].

Differences in SGOT and SGPT Levels

Serum SGOT and SGPT levels were measured in both control (K) and experimental groups (P1, P2, P3, P4, P5, and P6) using the enzymatic method. SGOT values in the control group (104.61–160.02 U/L) were used as the reference for normal levels in male Wistar rats (Rattus norvegicus), as no diabetogenic agents were administered. Statistical analysis revealed no significant differences ($p = 0.199$) among groups. However, compared with the control value (112.32 U/L), treatment groups induced with ALX (P1, P2, P3) and STZ (P4, P5, P6) displayed varying patterns.

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Group P1 (ALX 120 mg/kgBW) showed an increase in SGOT (118.75 U/L), but levels decreased in group P2 (ALX 150 mg/kgBW; 107.00 U/L) and further in group P3 (ALX 180 mg/kgBW; 104.10 U/L). The elevated SGOT observed in P1 indicates that the initial ALX dose elicited a strong response, potentially elevating SGOT above normal values. However, higher doses (P2 and P3) resulted in decreased SGOT, suggesting a regulatory mechanism against oxidative stress triggered by higher ALX doses, involving enhanced activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This indicates the development of ALX resistance, where antioxidant activity increases to reduce ROS accumulation and mitigate cellular damage[23].

In contrast, STZ-induced groups (P4, P5, P6) demonstrated an ascending pattern of SGOT levels proportional to the dose. Levels increased sequentially from P4 (20 mg/kgBW; 119.45 U/L) to P5 (40 mg/kgBW; 159.00 U/L), and further to P6 (60 mg/kgBW; 185.60 U/L). This progressive increase reflects the dose-dependent hepatotoxicity of STZ, leading to more severe hepatic damage[12].

For SGPT, the reference value for normal male Wistar rats was derived from the control group (70.41–89.48 U/L). Statistical analysis showed a significant difference ($p = 0.001$) between the control and experimental groups. Groups P1 (47.40 U/L), P2 (46.80 U/L), P3 (60.85 U/L), P4 (54.50 U/L), and P6 (136.50 U/L) differed significantly from the control group (75.15 U/L). Only group P5 (STZ 40 mg/kgBW; 87.30 U/L) showed no significant difference from the control. ALX-induced groups (P1, P2, P3) and one STZ group (P4) exhibited lower SGPT levels compared to the control, while groups P5 and P6 demonstrated elevated SGPT values.

When analyzed by a diabetogenic agent, STZ-induced groups (P4, P5, P6) showed a dose-dependent increase in SGPT, whereas ALX-induced groups (P1, P2, P3) demonstrated lower levels compared to the control. This suggests distinct mechanisms, with ALX resistance involving protective responses in hepatic tissue[23]. Previous studies have shown that ALX induction in rats enhances antioxidant enzyme levels and activity in response to oxidative stress[24-26].

SGPT examination is more specific for evaluating acute inflammatory conditions in the liver, as it increases when hepatocyte membranes are damaged, causing cytoplasmic components to leak into the bloodstream[27,28]. SGOT, on the other hand, tends to increase when mitochondrial damage occurs, indicating chronic liver injury[27,28]. This may explain the absence of significant differences in SGOT among groups, as evaluation was performed after 14 days. Compared with SGPT, SGOT levels were relatively higher, since SGOT is also present in other organs such as kidneys, cardiac muscle, skeletal muscle, brain, and erythrocytes. Thus, changes in SGOT may reflect not only liver injury but also cumulative effects in other organs due to the systemic toxicity of ALX and STZ[23].

Limitations of the Study

This study has several limitations. First, the duration of observation was limited to 14 days, which may not fully capture the long-term hepatotoxic effects of alloxan and streptozotocin. Second, the evaluation of liver injury was based primarily on histopathological scoring and serum SGOT/SGPT levels; additional biochemical or molecular markers of oxidative stress and apoptosis were not assessed. Future studies with longer observation periods, broader biomarker assessments, and inclusion of both sexes are warranted to provide a more comprehensive understanding of the hepatotoxic effects of diabetogenic agents.

CONCLUSION

The selection of diabetogenic agents between alloxan (ALX) and streptozotocin (STZ) should be made judiciously based on the variables to be observed. Histopathological examination of the liver using the Manja Roenigk scoring system revealed significant differences between the experimental and control groups; however, no substantial differences were observed between ALX and STZ at equivalent doses. Biochemical assessment showed that ALX administration may induce resistance, resulting in SGOT and SGPT values below the normal range, whereas STZ tended to produce more consistent elevations in these enzyme levels. In conclusion, STZ is superior to ALX as a diabetogenic inducer in Wistar rats, as it yields more reliable biochemical and histopathological outcomes.

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ETHICAL APPROVAL

This study received ethical clearance from the Health Research Ethics Committee (HREC), Faculty of Medicine, Diponegoro University, Semarang (Approval Number: 041/EC/KEPK/FK-UNDIP/V/2024).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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