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Original Article

# Subtle Intricacies Identified during Streptozotocin-Induced Diabetes in Wistar Rats

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## ABSTRACT

**Aim:** This study aimed to establish the dose of streptozotocin required to induce Type -1 diabetes in Wistar rats. **Background:** Streptozotocin is currently employed worldwide to induce insulin-dependent diabetes mellitus also known as Type 1 diabetes mellitus in experimental animals. Though many reports on the use of streptozotocin induction of diabetes are reported in the literature, they were not reproducible. Moreover, there was no mention of the mortality associated with the same as well as the conditions followed during the study. **Materials and Methods:** In the present study, the dose, route, and solvent used for streptozotocin were investigated. Various doses of streptozotocin 55, 50, 40, and 35mg/kg dissolved in either freshly prepared cold 10mM sodium citrate buffer (pH 4.5) or normal saline solution was administered intraperitoneally as well as intravenously. For intraperitoneal administration, the dose-volume was 10mL/kg whereas for intravenous administration the dose-volume was 2mL/Kg. Different routes were employed to ascertain the cause of mortality for which an autopsy was performed. Besides mortality rate was also determined. **Results and Discussion:** The findings of the study revealed that a 35-40mg/kg dose of streptozotocin showed less percentage mortality and successful induction of diabetes. **Conclusion:** Mortality (10-20%) was observed at a dose of 35-40mg/kg streptozotocin. Therefore, streptozotocin (35-40mg/kg) was confirmed to be safe and effective for the induction of diabetes in Wistar rats. This paper highlights subtle intricacies observed during induction of diabetes in Wistar rats using streptozotocin

**Keywords:** Male Wistar rats, Streptozotocin, Type-1 diabetes, 5% dextrose, Mortality, Normal saline solution.

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## INTRODUCTION

Streptozotocin (STZ) is currently employed worldwide to induce insulin-dependent diabetes mellitus (IDDM), also known as Type 1 Diabetes Mellitus (T1DM) in experimental animals. However, despite meticulously following protocols for STZ induction of diabetes as published in the literature, a high percentage of mortality was observed in experimental animals. Alarmed with the high percentage of mortality, the authors decided to put across their findings which could help researchers attempting to induce diabetes in experimental animals as none of the papers mentioned the mortality rate after STZ administration. Also, certain conditions to be followed post-STZ administration was not documented. Based on the literature survey conducted, various doses of STZ have been employed (40,[1-3] 45,[4-8,] 50,[9] 55,[10-13] 60,[14-18] 65[19-22] mg/kg), (Table 1) to induce diabetes in Wistar rats. STZ was mostly dissolved in 10 mM sodium citrate buffer (pH 4.5) and a few instances in normal saline solution.[23-28] Though 10mM sodium citrate buffer pH (4.5) was commonly employed as a solvent to dissolve STZ, the mortality percentage and cause of mortality associated with these methods were not documented. Therefore, researchers attempting STZ for diabetes induction face problems due to a lack of information regarding mortality and experimental conditions to be followed. This study was carried out to establish diabetes in Wistar rats following the STZ dose reported in the literature. In this study, we investigated mortality percentage and cause of mortality with the administration of STZ in various doses reported in the literature. Moreover, we also investigated suitable solvents for STZ. STZ was injected intravenously as well as intraperitoneally in Wistar rats to compare and ascertain the cause of mortality following STZ injection.

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**Table 1: STZ doses employed according to various literature reports.**

| Streptozotocin (mg/kg) | References |
|---|---|
| 40 | 1-3 |
| 45 | 4-8 |
| 50 | 9 |
| 55 | 10-13 |
| 60 | 14-18 |
| 65 | 19-23 |

## MATERIALS AND METHODS

### Materials

Streptozotocin purity (98%) was purchased from Sigma Aldrich (India). Normal saline (0.9%) was purchased from KMC hospital pharmacy, Manipal (India). Citric acid monohydrate and trisodium citrate dihydrate was purchased from Merck life Sciences. Mumbai (India). Dextrose solution was purchased from Finar Limited. Gujarat, India. Glucometer (Contour) was purchased from Ascensia Diabetes Care (India).

### Induction of diabetes

Animal experiments were carried out following approval from the Institutional Animal Ethical Committee (IAEC/KMC/20/2019), Kasturba Medical College, MAHE, Manipal. Male Wistar rats, 250±20 g, were used in this experiment. Animals were acclimatized for 7 days in laboratory conditions before the experiment and kept at (20-25°C, 75±5% humidity, 12:12-hr light: dark cycle) with unlimited access to food and water. All rats were fasted for 12 hr and had access to water before STZ dosing.

The animals were divided into nine groups, with each group consisting of eight animals. ($n$=8). Group 1: received a single-dose intraperitoneal injection (i.p) of 55mg/kg STZ dissolved in freshly prepared cold (10mL/kg) 10mM sodium citrate buffer (pH 4.5). Group 2: received a single-dose i.p. injection of 55mg/kg STZ dissolved in cold normal saline. Group 3: received a single-dose i.p injection of 50mg/kg STZ dissolved in freshly prepared cold (10mL/kg) 10mM sodium citrate buffer (pH 4.5). Group 4: received a single-dose i.p injection of 50mg/kg STZ dissolved in cold normal saline solution. Group 5: received a single-dose i.p injection of 40mg/kg STZ dissolved in freshly prepared cold (10mL/kg) 10mM sodium citrate buffer (pH 4.5). Group 6: received a single-dose i.p injection of 40mg/kg STZ dissolved in cold normal saline solution. Group 7: received a single-dose i.p injection of 35mg/kg STZ dissolved in freshly prepared cold (10mL/kg) 10mM sodium citrate buffer (pH 4.5). Group 8: received a single-dose of i.p injection of 35mg/kg STZ dissolved in cold (10mL/kg) normal saline. Group 9: received a single- dose of intravenous injection (i.v) of 35mg/kg STZ dissolved in the cold (2mL/kg) normal saline.

STZ was solubilized in either fresh cold normal saline or freshly prepared cold 10mM sodium citrate buffer pH (4.5) and injected in dark conditions within 5 min of preparation.

Following STZ administration, 5% w/v dextrose solution bottles were immediately placed in cages for up to 48 hr. Blood glucose levels were monitored for 3days post-STZ administration using a glucometer. Rats showing non-fasting blood glucose levels over 400mg/dL were considered diabetic. The mortality rate was determined and the cause of mortality was ascertained by autopsy.

## RESULTS AND DISCUSSION

There are many studies reported in the literature using various doses of STZ for the induction of diabetes. In our study mortality was the main concern for fixing the STZ dose. Hence, we started with STZ doses reported in the literature for inducing diabetes. Consequently, we have reported mortality observed with the administered STZ doses.

According to Alain Junod[24] various doses of STZ (25-100mg/kg) were tested to investigate the association between STZ dosage and metabolic activity. Based on these findings severe hyperglycemia was reported 2 to 4 hr after STZ administration, while severe hypoglycemia was observed 7 hr post-STZ administration. Despite the fact that mortality was observed, the mortality rate was not reported.

Since hypoglycemia was seen at 7 hr post-STZ administration in the study reported by Junod *et al* and as per literature search, we investigated 55 and 50mg/kg STZ i.p doses dissolved in the cold (10mL/kg) 10mM sodium citrate buffer (pH 4.5) and cold normal saline respectively. Dextrose (15%) solutions were placed in cages at 7 hr post-STZ administration in our study.

On the contrary, Aloud AA[2] used 20% glucose to prevent mortality. However, 100% mortality was observed with 55 and 50mg/kg STZ doses in our study, despite providing dextrose 15% solution to rats. Kotian SR[1] used 5% glucose post-STZ 40mg/kg and Bagdas D, *et al.*[5] used 6% sucrose post-STZ 45mg/kg immediately. However, there was no mention of mortality in their studies.

The next trial was focused on placing dextrose solution (5%) immediately as reported in the study of Kotian SR[1] and Bagdas D, *et al.*[5] The mortality rate was reduced to 50% and was observed during 48 to 60 hr post STZ dosing (for STZ dissolved 10mM sodium citrate buffer (pH 4.5) as well as normal saline).

Based on these studies, it was concluded that STZ doses (55, 50mg/kg) were not safe for induction of diabetes in male Wistar rats. Therefore, a reduced dose (40mg/kg) was administered (i.p) and dextrose 5% was placed immediately. With this dose, 20% mortality was observed while the remaining 80% of rats showed elevated blood glucose levels confirming the onset of diabetes.

**Table 2:** Percentage of mortality observed at various intervals with different doses (i.p, i.v) of STZ.

| Sl. No | Treatment Group (mg/kg) | Percentage of Mortality (%) | Time of mortality (hr) |
|---|---|---|---|
| 1 | 55(mg/kg) (i.p route) di sodium citrate buffer (pH4.5) | 50% | 48-72 |
| 2 | 55(mg/kg) (i.p route) normal saline | 50% | 48-72 |
| 3 | 50(mg/kg) (i.p route) di sodium citrate buffer (pH4.5) | 50% | 48-72 |
| 4 | 50(mg/kg) (i.p route) normal saline | 50% | 48-72 |
| 5 | 40(mg/kg) (i.p route) di sodium citrate buffer (pH4.5) | 20% | 62-86 |
| 6 | 40(mg/kg) (i.p route) normal saline | 20% | 62-86 |
| 7 | 35(mg/kg) (i.p route) di sodium citrate buffer (pH4.5) | 10% | 62-120 |
| 8 | 35(mg/kg) (i.p route) normal saline | 10% | 62-120 |
| 9 | 35(mg/kg) (i.v route) normal saline | 50% | 48-72 |

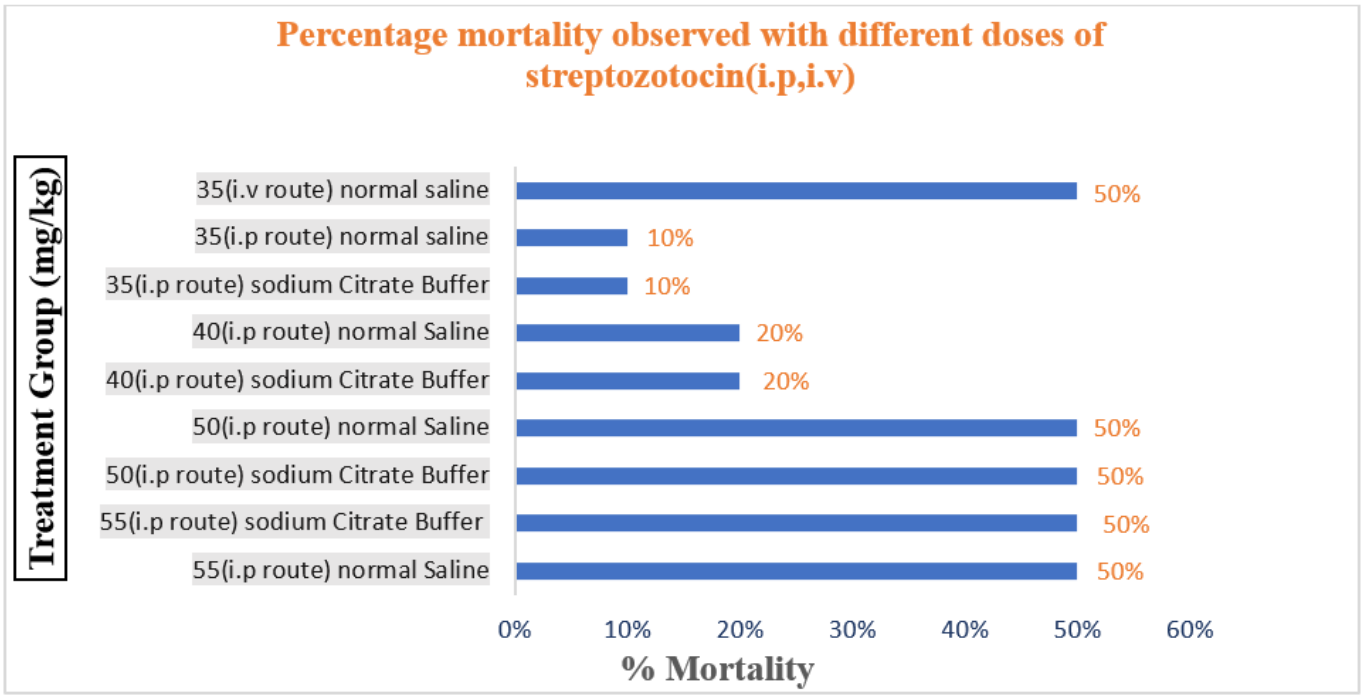


**Figure 1:** Percentage mortality observed with different doses of streptozotocin (i.p, i.v).

The time at which mortality was previously observed was delayed and was seen during 60 to 84 hr post STZ dosing.

Based on these findings and to reduce the mortality, a reduced STZ dose (35mg/kg) in either sodium citrate buffer (pH 4.5) or saline was administered (i.p) and dextrose 5% was placed immediately. This resulted in 10% mortality but the mortality was delayed (96 hr) and the remaining 90% of rats developed diabetes.

It can be concluded from the results of these batteries of experiments that the solvent for STZ did not influence the induction of diabetes as similar results were obtained. STZ 35mg/kg was demonstrated to be a safe and suitable dose for induction

of diabetes. The onset of diabetes was confirmed by measurement of the blood glucose concentration with a glucometer 86 hr post STZ dosing. The mortality rate was lowered and the time for mortality was longer at the STZ dose of 35mg/kg. Mortality was observed between 72 to 120 hr post STZ dosing. The results of this study ascertain that a 35mg/kg dose is appropriate for the induction of diabetes in male Wistar rats. Providing dextrose (5%) immediately following STZ dosing is very crucial to avoid mortality. Moreover, both solvents cold (10mL/kg) 10mM sodium citrate buffer pH 4.5 and (10mL/kg) normal saline solution were capable of serving as a solvent for STZ. The outcome of the trials with varying doses of STZ with respective mortality and time for mortality is shown in (Table 2).

Furthermore, to verify the cause of mortality in STZ-dosed rats, STZ (35mg/kg) was injected through the i.p as well as the i.v route. No evident changes in the organs were observed in autopsied rats irrespective of routes employed. Finally, the results of this study confirm that rats died majorly due to STZ toxicity and not due to different routes of administration. During the investigation, polyuria, polydipsia, and polyphagia were identified in diabetic rats.

To confirm whether the STZ dose (35mg/kg) was optimum for the induction of diabetes, the method was repeated. With the same dose, the STZ dose (35mg/kg) was freshly prepared in both solvents and administered intraperitoneally and dextrose 5% was placed immediately.

The results confirmed that the method was reproducible.

A literature review on the use of STZ for induction of diabetes results in several reports mentioning STZ doses in the range of 40-65mg/kg to induce diabetes. However, percentage mortality was not reported in the references cited. Though the STZ doses reported in the literature were able to induce diabetes, the rats (50%) did not survive for more than 48-72 hr in our study. In this study, we successfully induced type 1 diabetes at 35mg/kg STZ dissolved in cold (10 mL/kg) normal saline solution by i.p injection in rats as shown in Figure 1. The findings of our study also ascertained the importance of providing dextrose immediately to the rats following STZ dosing.

## CONCLUSION

Induction of diabetes using various doses of STZ (55, 50, 40, 35mg/kg) in two different solvents was investigated. The influence of the solvent and route of administration on the induction of diabetes with STZ was evaluated. STZ was either dissolved in (10mL/kg) sodium citrate buffer (pH. 4.5) or normal saline injected intraperitoneally in male adult Wistar rats. Mortality (50%) was observed at 55 and 50mg/kg STZ. Mortality (10-20%) was observed at a dose of 35-40mg/kg STZ. Therefore, STZ (35-40mg/kg) was confirmed to be safe and effective for the induction of diabetes in Wistar rats. The study also established the necessity of providing dextrose immediately following STZ dosing. The concentration of dextrose (5%) and the time of providing dextrose (immediately) were crucial in avoiding mortality during induction of diabetes.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

## ABBREVIATIONS

**STZ:** Streptozotocin; **T1DM:** Type-1 diabetes mellitus; **IDDM:** Insulin dependent diabetes mellitus.

## SUMMARY

The study aimed to ascertain the dose of STZ required to induce diabetes in Wistar rats and the conditions to be followed to avoid mortality. The various doses of STZ (55, 50, 40, 35 mg/kg) solubilized either normal saline or 10mM sodium citrate buffer (pH 4.5) through intraperitoneal and intravenous administration were investigated. At STZ (35-40mg/kg) intraperitoneal injection, followed by providing a 5% dextrose solution immediately resulted in less mortality (10-20%). The findings of our study strongly suggest that induction of Type 1 diabetes in male Wistar rats with 35-40mg/kg STZ with minimum mortality is a viable option.

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