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Dexamethasone and 5% NaCl Solution Induce Hypertension in *Sparangue dawly* Male Rats

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ABSTRACT

High blood pressure can be caused by excess salt intake Dexamethasone is a potent anti-inflammatory drug, but the long-term administration can cause hypertension. This study aims to determine the accurate time and dose that cause hypertension in rat models by administration of a combination of dexamethasone and 5% NaCl solution. The control group was administrated with aquadest orally, 3 test groups were administrated with dexamethasone at a doses of 0.02mg/kg BW, 0.03mg/kg BW, and 0.5mg/kg BW intraperitonially (i.p) for 28 days. A 5% NaCl solution were administrated instead of drinking water to the test group. Blood pressure and body weight were measured weekly for 28 days. Results of the study show that Dexamethasone at a dose of 0.02mg/kg BW caused hypertension on day-28 where the rats blood pressure increase to 148mmHg/103mmHg (±1.9/±3.1) ($P<0.05$) compared to control rats and the weight decline by 90 grams. Dexamethasone 0.03mg/kg BW caused hypertension on day-21, with the increase of rats blood pressure at144mmHg/101mmHg (±2,6/±3.2) ($P<0.05$) compared to control and the weight decrease by 83 grams. Dexamethasone 0.5mg/kg BW caused hypertension on day-7, the rats blood pressure rise to 146mmHg/103mmHg (±1.6/1.9) ($P<0.05$) compared to control and the weight decrease by 69 grams. As conclusion, Dexamethasone at dose of 0.5mg/kg BW and NaCl 5% cause hypertension faster on day 14 compared to dexamethasone at dose of 0.02mg/kg BW and NaCl 5% which cause hypertension slower after 28 days of administration.

Keywords: Hypertension; dexamethasone; NaCl 5%

INTRODUCTION

Hypertension is a multifactorial chronic condition characterized by a persistent rise in systolic and diastolic blood pressure (BP) (Whelton et al., 2018). Hypertension is defined as a condition in which the systolic blood pressure (SBP) is greater than 140 mmHg and/or the diastolic blood pressure (DBP) is greater than 90 mmHg (Bergler-Klein, 2019).

Glucocorticoids are steroid hormones that regulate a variety of physiological functions, including energy metabolism, immunological response, blood pressure, mood/memory, and stress reactions (Kapugi & Cunningham, 2019). Glucocorticoids (GCs) are used to treat a variety of inflammatory diseases, immunosuppressive agents and cancer, as well as to avoid organ transplant rejection (Vandewalle et al., 2018). High doses and long-term use of these drugs, on the other hand, are linked to major side effects such cardiovascular events, hypertension, diabetes, bone loss, insulin resistance, glucose

intolerance, dyslipidemia and fractures (Joukar et al., 2017; Moghadam-Kia & Werth, 2010).

Dexamethasone (Dex) is one of synthetic glucocorticoids that are important in the treatment of inflammatory diseases. An increase in blood pressure is one of the side effects of Dex therapy. The fundamental mechanism causing dexamethasone-induced hypertension is a reduction in endothelium-produced nitric oxide (NO) (Tobias et al., 2015).

Administration of dexamethasone dose 0.3mg/kg BW in drinking water of test animals may increase blood pressure (Soto-Piña et al., 2016). Induction of hypertension in test animals can be done by giving dexamethasone 0.5mg/kg BW or according to the dose in the preliminary test (Kepala, 2021).

Sodium is a necessary nutrient for normal bodily function and health. However, regardless of blood pressure, increasing salt intake is linked to an increased risk of acute coronary events and cardiovascular mortality (Mente et al., 2021; Patik et al., 2021). High salt intake can promote endothelial dysfunction by forming free radicals (ROS) and decreasing the bioavailability of nitric oxide (NO) (Patik et al., 2021).

The endothelium plays a key role in vascular function through a variety of mechanisms, including the synthesis and release of autocrine and/or paracrine chemicals (Cameron et al., 2016; Harvey et al., 2015; Silva et al., 2019). Under physiological conditions, vascular NO is primarily produced by endothelial nitric oxide synthase (eNOS) (Xia et al., 2014).

Endothelial dysfunction is defined by changes in the production or bioavailability of vasoactive molecules, particularly vasodilators like nitric oxide (NO) and vasoconstrictors like angiotensin and endotelin (Harvey et al., 2015). Other molecular effects and changes in blood vessel reactivity result in increased oxidative stress and activation of proinflammatory signaling pathways, which contribute to endothelial dysfunction (Cameron et al., 2016; Michael A. & Guillermo, 2016). Induction of hypertension in test animals can be done by giving 4% NaCl orally (BPOM RI, 2019). In this study, the NaCl used was 5%, this was done with the hypothesis that the greater the concentration of NaCl used, the faster hypertension occurs.

Based on the description above, the administration of dexamethasone and NaCl can be used for the formation of animal models of hypertension. This study was conducted to determine how long it takes and effective dose to form an animal model of hypertension induced by a combination of dexamethasone and 5% NaCl solution, the addition of this 5% NaCl solution is expected to accelerate the occurrence of hyperthesis compared to the administration of dexamethasone alone.

This research is considered necessary to provide information to researchers or students who will conduct antihypertensive tests on a chemical drug compound or natural material that requires information related to the method of developing a hypertension animal model formation with endothelial dysfuction pathways.

Correlation test will also be carried out between the effect of dexamethasone dose on the speed of occurrence of hypertension and the length of life span of test rats during induced with dexamethasone and NaCl 5%, this needs to be done because based on research that has been reported by Kamphuis et al., 2007 that the administration of dexamethasone can cause long-term cardiovascular, renal morbidity, and reduced life span may be due to long-lasting cardiomyocyte hypertrophy, hypertension and end-stage nephropathy (Kamphuis et al., 2007).

METHODS

Animals

Male rats of the *Sprague dawley* strain weighing 150–300 grams and aged 2–3 months obtained from UD. Wistar (Test animal breeders) Yogyakarta used in this study. Rats are placed in cages with room temperature kept in the range of 24-26°C, humidity 60-65%, and lighting is set to 12 hours of light cycle and 12 hours of dark cycle. Feeding and drinking

water by ad libitum. Before conducting animal studies test in acclimatization first for 1 week. The Ethics Committee of the Faculty of Medicine, University of Indonesia, has approved the research protocols and animal handling procedures. (KET1238/UN2.F1/ETIK/PPM.00.02/2021)

Chemicals

Dexamethasone (Bhernofarm pharmaceutical company), 0.9% saline (Otsuka), aquadest, NaCl (salt).

Equipment

CODA (Kent scientific) is used to measure the blood pressure of rats in a non-invasive manner, syringe 1 ml (one med), scales (mettler toledo).

Experimental Design

The four groups of test animals which are divided randomly, each group consisting of 6 test animals. Group 1 was the control normal, given aquadest orally. Three treatment groups, namely group 2, 3, and 4 received dexamethasone 0.02mg/kg BW, 0.03mg/kg BW and 0.5mg/kg BW intraperitonially (i.p).

Experimental Procedures

Group 1 was the control normal, given aquadest orally, group 2 treated with dexamethasone 0.02mg/kg BW i.p (intraperitonially), group 3 received dexamethasone 0.03mg/kg BW i.p, and group four obtained dexamethasone 0.5mg/kg BW i.p once daily for 28 days. 5% NaCl solution was substituted as drinking water for test group. Blood pressure and body weight were measured weekly for 28 days.

Data Analysis

The data obtained in this study were analyzed with the application of SPSS version 26, One-way ANOVA was used to evaluate data including homogeneity and normality tests with kolmogorev-smirnov or shapiro-wilk, then continued with the Tukey HSD post-hoc test to determine meaningful differences between the control normal group and the test group. The significance threshold was set at P<0,05.

RESULTS AND DISCUSSION

Male rats of the *sparangue dawly* strain were employed as test subjects in this investigation with an average body weight of 150-300 grams, this was done because young adult male rats have greater BP than females (SD) (Lerman et al., 2019). Before being injected with dexamethasone and given a 5% NaCl solution instead of drinking water, the blood pressure of the test rat in each group was measured to ensure that all test rats had normal blood pressure.

The results of induction with dexamethasone and 5% NaCl solution for one month showed that the systolic blood pressure data obtained were homogeneously distributed (P=0.786) based on the test of homogeneity of variences and the shapiro-wilk test showed data normal distributed (P=0.659). Diastolic blood pressure is homogeneously distributed (P=0.304) and routinely distributed (P= 0.804). Mean arterial pressure (MAP) data are distributed homogeneously (P=0.420) and normally distributed (P=0.514). The body weight of the rat was homogeneously distributed (P=0.53) and normally distributed (P=0.772).

Hypertension most quickly occurred in the group receiving a dose of 0,5mg/kg BW as stated in figure 1, figure 2, and table 1 where systolic and diastolic blood pressure increased on day 7 by 24/22 (+-1,6/+-1,9) mmHg, post-hoc test show (P=0.000) significance different compared to the control normal group. Mean arterial pressure (MAP) value of 116 (P=0.000) constantly increased until day 14. The results are in accordance with research that has been conducted by Garmana et al., 2018 (Garmana et al., 2018). The weight of rats in this group also decreased by an average of 34 grams every week shown in figure 3. However, hypertension in this group persists only for 7

days and the test animals were only able to survive for 14 days.

Dexamethasone dose of 0.03mg/kg BW cause hypertension on day 21, systolic and diastolic blood pressure increased by 27/19 (+-2,6/+-3,2) mmHg, post-hoc test (P=0.000) with a MAP value of 115 (P=0.000) significance different compared to the control normal group and constantly increased until day 49. These results are slightly different from those that have been carried out by Joukar et al., 2017 where systolic and diastolic blood pressures increased after animal tests were induced for 11 days subcutaneously (Joukar et al., 2017). The formed hypertension lasted only for 28 days, and the test animal was able to survive for 49 days. The test animals lost weight weekly on average by 21 grams.

Dexamethasone dose of 0.02mg/kg BW causes hypertension at the latest on day 28, systolic and diastolic blood pressure increased by 30/21 (+-1,9/+-3,1) mmHg (P=0.000) with MAP value of 117 (P=0.000) significance different compared to the control normal group on the same day. This is in line with the research that has been carried out by Ugusman et al., 2020 (Ugusman et al., 2020). The hypertension formed was only able to last for 28 days, starting from day 28 to day 56 and test animals in this group were able to survive longer than groups 2 and 3, which was more than 56 days. The body weight of rats in this group decreased by an average of 23 grams per week.

The systolic, diastolic, MAP, and weight blood pressure data shown in Figures 1, 2, 3 and Table 1 were the results of observations for 28 days, while for the dexamethasone group at a dose of 0.02 mg/kg BW observations continued for up to 60 days to see the life span of the test rats, blood pressure data, after the 28th day were not shown in gerafik because the time it took until the occurrence of hypertension in this group was already known according to the purpose of the study.

All induction dose groups demonstrated that dexamethasone and salt caused test animals to lose weight, this is consistent with research by Adeosun et al., 2021 and research that has been carried out by Filippopoulou et al., 2022 and El-Sonbaty et al. 2019 shows that dexamethasone lost weight in test rats and mice (Adeosun et al., 2021; El-Sonbaty et al., 2019; Filippopoulou et al., 2022). Another study conducted by Saganuwan et al., 2010 showed that giving salt solution to induce hypertension in rats can lose weight (El-Sonbaty et al., 2019).

There is a correlation between the dose of dexamethasone used to the speed at which the hypertension animal model is formed as stated in Figure 4, where the correlation test shows that the value of R = 0.90 is close to 1 which means that there is a strong relationship between the dose to the occurrence of hypertension, where the greater the dose ussed, the faster the occurrence of hypertension and the smaller the dose of dexamethasone used, the slower the occurrence of hypertension. In addition, Figure 5 also shows that there is a correlation between the dose of dexamethasone used to the length of life span of the test rat used, where the correlation test results show a value of R = 0.98 which means that there is a fairly strong relationship between the dose of dexamethasone and the length of life span of the test rat, whereas the test rat's life span is shorter or it dies more quickly when a higher dose of dexamethasone is given, and the test rat's life span is longer when a lower dose is used.

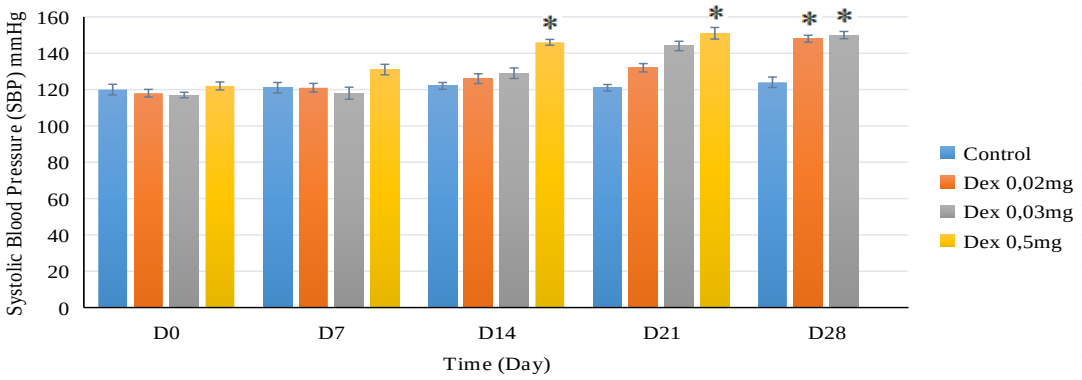

Figure 1. Systolic blood pressure of each group
These data are presented as a mean ± SEM of each group (n = 6). (≥140) *P < 0.05 significance different compared to the control normal group on the same day. Abbreviation: D: Day, Dex: Dexametason (0,02mg, 0,03mg, 0,5mg/kg body weight).

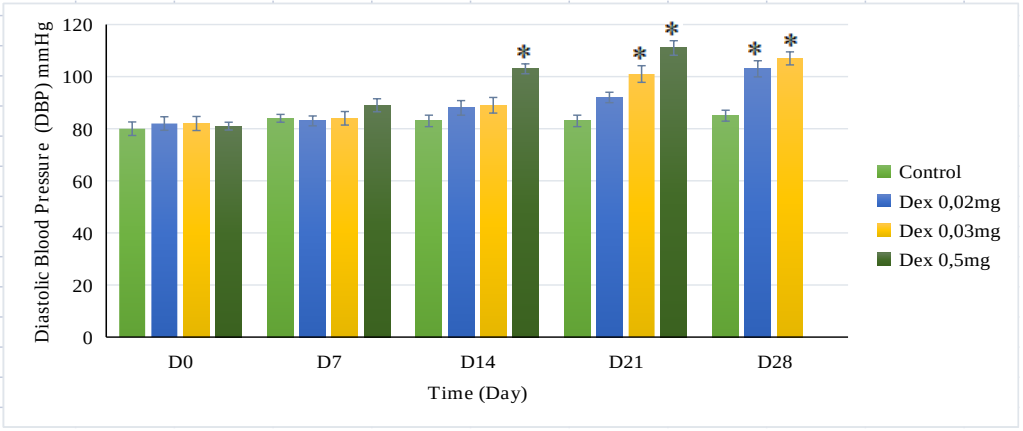

Figure 2. Diastolic blood pressure of each group
These data are presented as a mean ± SEM of each group (n = 6). (≥90) P < 0.05 significance different compared to the control normal group on the same day. Abbreviation: D: Day, Dex: Dexametason (0,02mg, 0,03mg, 0,5mg/kg body weight).

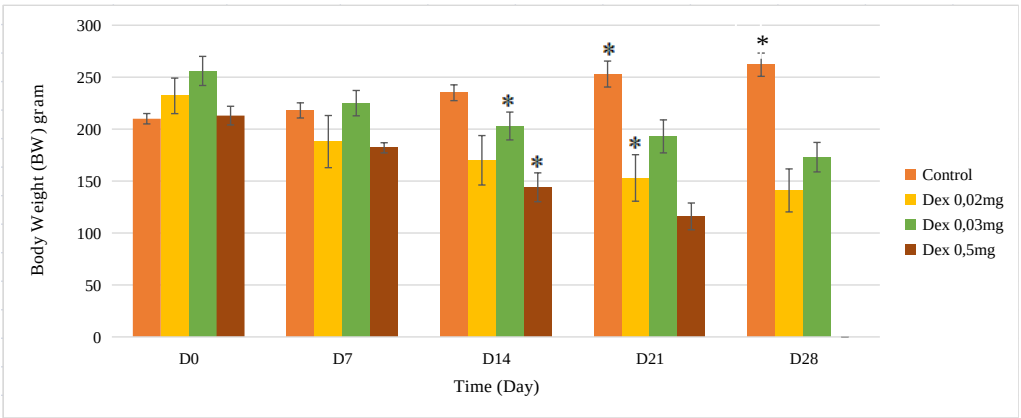

Figure 3. Body weight (BW) of each group
The weight in the control normal group increased while in the dexamethasone (Dex) group decreased. These data are presented as a mean ± SEM of each group (n = 6). *P < 0.05 significance different compared to previous week's data.

Table 1. Mean Arterial Pressure (MAP) mmHg

Group	D0	D7	D14	D21	D28
Control	93 ± 2,4	95 ± 1,6	96 ± 1,7	95 ± 1,9	98 ± 1,5
Dex 0,02mg	94 ± 1,8	95 ± 1,8	100±1,8	105± 1,6	117± 2,6*
Dex 0,03mg	93±1,4	96±3,1	102±2,3	115±2,4*	121± 2,5*
Dex 0,5mg	94 ± 1,3	116 ± 2,7*	124 ± 2,4*	-	-

These data are presented as a mean ± SEM of each group (n = 6). (≥90) *P < 0.05 significance different compared to the control normal group on the same day. Abbreviation: D: Day, Dex: Dexametason (0,02mg, 0,03mg, 0,5mg/kg body weight).

Based on systolic, diastolic, and mean arterial pressure data obtained showed that dexamethasone and 5% NaCl (salt) solution were effective for forming hypertensive animal model. however, when compared to the research that has been carried out by Ugusman et al., 2020 which used a dose of dexamethasone 0.02 mg/kg BW without the administration of a 5% NaCl solution instead of drinking water and caused hypertension after 28 days of administration, the addition of salt solution in this study did not accelerate the occurrence of hypertension. On the other hand, dexamethasone causes a decrease in nitric oxide (NO) levels only through a down-regulation of eNOS mRNA (Blecharz-Lang & Burek, 2017). Purpose of the addition of a 5% NaCl solution in this study is to cause the uncoupling of eNOS so that it actually lowers the level of nitric oxide and causes endothelial dysfunction (Li et al., 2016) as a result of the research that has been done by Satoh et al., 2010 (Satoh et al., 2010).

Dexamethasone, by acting on the mitochondrial electron transport chain, NAD(P)H oxidase, and xanthine oxidase, has been demonstrated to induce ROS overproduction in human endothelial cells. An increase in the amount of ROS can trigger hypertension (Tain & Hsu, 2022; Yu et al., 2021). Reducing NO bioavability and causing oxidative stress in the vasculature, contributing to endothelial cell damage. Acute exposure to dexamethasone in experimental rats inhibits endothelial nitric oxide synthase, which prevents NO synthesis in the endothelium (eNOS) (Macleod et al., 2021).

Furthermore, Excess sodium in the diet increases superoxide (O^{2-}) by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, while inhibiting cytosolic superoxide dismutase and mitochondrial superoxide dismutase (SOD-1) (SOD-2). Nitric oxide (NO) cannot diffuse into the VSM because of the easy way in which it reacts with O^{2-}. The ensuing peroxynitrite (ONOO) oxidizes tetrahydrobiopterin (BH4), which causes eNOS to become uncoupled, further causing decreases in (NO) and rises in O^{2-} (Krajina et al., 2022; Patik et al., 2021). Reduced levels of nitrit oxide (NO) in the endothelium leads to endothelial dysfunction, which is involved in the pathogenesis of hypertension (Ugusman et al., 2020).

Weight loss in test animals is caused by the ability of dexamethasone to trigger the release of leptin from adipose tissue, which leptin regulates body weight by lowering the feeding intake of the test animal, causing weight loss (Frühbeck et al., 2017; Malkawi et al., 2018)

The number of rat that died during the study, especially in the highest dose of dexamethasone group, namely 0.5 mg/kg BW, has not been determined the main cause, this is similar to the research that has been carried out by Jouda, 2016 secured in his study there were 21 test rat that died without knowing the cause (Jouda, 2016). However, if referring to the results of research that has been done that dexamethasone causes weight loss which causes test animals to become weak, lethargic, and according to existing references it states that dexamethasone has an immunosuppressant effect on decreasing the body's immune system so that the body becomes susceptible to disease and easy to die (Giles et al., 2018).

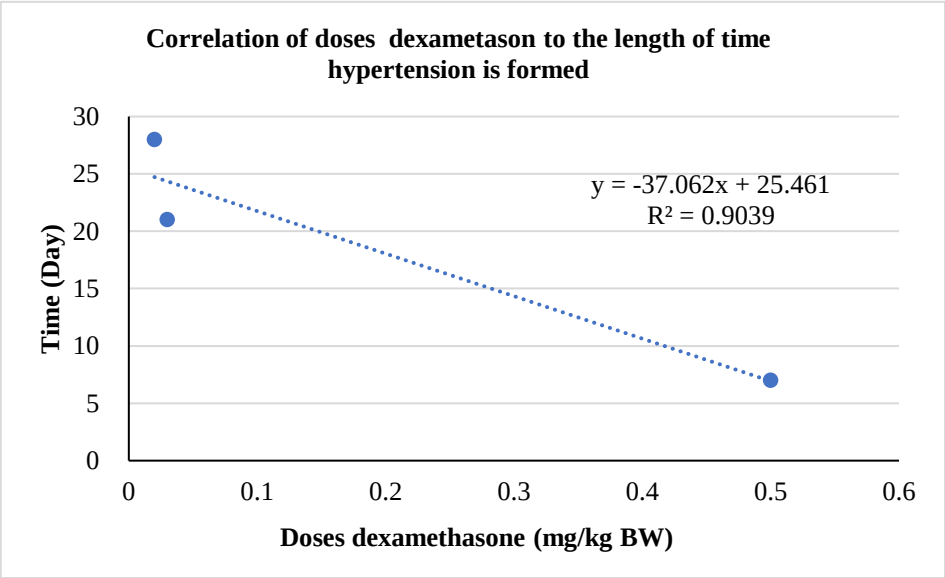

Figure 4. Correlation of doses to the length of time hypertension is formed

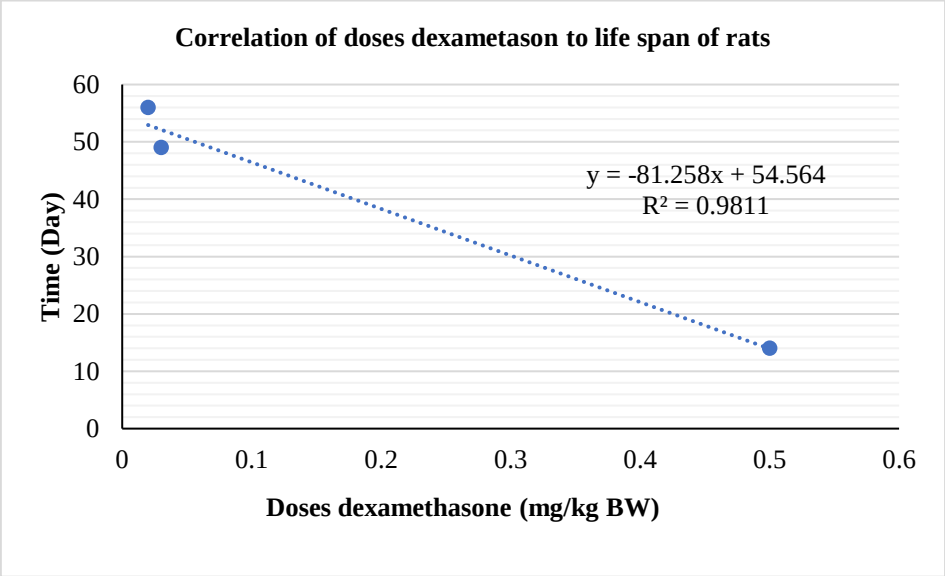

Figure 5. Correlation of doses to life span of rats

CONCLUSIONS

According to the research's findings, it can be concluded that the combination of dexamethasone and sodium chloride 5% or salt is effective for forming hypertension animal models. Dexamethasone and 5% NaCl of the highest dose, namely 0,5mg/kg BW, causes hypertension the quickest, namely on the day 7 after administration. Subsequently, dexamethasone 0.03mg/kg BW caused hypertension on day 21. Furthermore, the lowest dose of dexamethasone 0.02mg/kg BW causes hypertension for the longest time, that is, after 28 days of administration, however, this dose is considered the most effective because test animals can survive longer than other test groups.

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CONFLICT OF INTEREST

The authors confirmed that there was no conflict of interest in the study

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