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Effect of low dose of niclosamide ethanolamine on morphometric parameters in isoprenaline-induced cardiac injury

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Abstract
Present study was undertaken to assess the effect of niclosamide ethanolamine on morphometric parameters in isoprenaline (ISP)-induced cardiac injury. Cardiac injury was induced by administering the isoprenaline at a dose of 20 mg/kg body weight through subcutaneous route for 14 days. Niclosamide ethanolamine was administered @ 1 mg/kg b.w. (intraperitoneally) on alternate days for initial eight days with daily dosing of ISP in treatment group. Control group and niclosamide alone group were received vehicle and niclosamide (@1 mg/kg b.w.; I.P. alternately for initial 8 days), respectively. On day 15th (after 24 hours of last dose of isoprenaline) mice were weighed and sacrificed under anaesthesia. Heart weight and tibial length of different group mice were measured. Study reveals that absolute heart weight and relative indices *viz*., heart weight to tibial length were increased in isoprenaline administrated group, which have been decreased by niclosamide ethanolamine treatment. In conclusion, niclosamide ethanolamine showed improvement in heart weight and heart weight to tibial length in isoprenaline-induced cardiac injury.

Keywords: Cardiac, isoprenaline, morphometric, niclosamide ethanolamine

Introduction
Cardiovascular diseases have emerged as global concern due to high prevalence, morbidity, disability, mortality and causing high economic losses (Mensah *et al*., 2019) [1]. In 2019, approximately 32% deaths of global deaths were shared by CVDs fatalities (WHO, 2021) [2]. According to Berenji and co-workers (2005) [3], cardiac hypertrophy is an adaptive response of cardiomyocytes to haemodynamic stress and exerts a compensatory role to preserve the cardiac functions by enhancing heart performance and reducing the wall tension of ventricles and oxygen consumption. The body's heart reacts to hemodynamic overload by hypertrophy to improve the contractility and lower the stress of ventricular wall, however, this adaptive hypertrophy eventually results in heart failure due to pathological remodeling (Nakamura and Sadoshima, 2018) [4]. Chronic stimulation of adrenoceptors by elevated level of circulating catecholamine is responsible for maladaptive cardiac remodeling, including myocardial hypertrophy, cardiac fibrosis and apoptosis, which may lead to the heart failure (Fu *et al.*, 2012) [5].
The oral anthelminthic drug, niclosamide is used for the therapy of parasitic infection that acts as an oxidative phosphorylation uncoupler and interferes with helminth's energy metabolism (Chen*et al.*, 2018) [6]. According to Fu and co-workers (2021) [7], niclosamide improved cardiac dysfunction, by stimulating the mitochondrial respiration of cardiac cell and decreasing the inflammatory cytokines in heart failure in transverse aortic constriction. Although, potential role of the niclosamide in various conditions including hypertension (Li *et al.*, 2017) [8], diabetes (Engin *et al.*, 2021) [9], liver injury (Esmail *et al.*, 2021) [10], neuroinjury (Cerles *et al.*, 2017) [11], oxidative stress (Jadhav *et al.*, 2020) [12], inflammation (Shivaji *et al.*, 2019) [13] have been reported. However, no study has assessed the effect of low dose of niclosamide on morphometric parameters in isoprenaline-induced cardiac injury.

Therefore, the present study was designed to assess the impact of niclosamide ethanolamine on morphometric parameters in isoprenaline-induced cardiac injury.

Materials and Methods

Experimental study

Apparently healthy male Swiss albino mice weighing 25-30 gm were procured from Laboratory Animal Resource Section, ICAR-Indian Veterinary Research Institute, Izatnagar. Animals were kept for acclimatization for a week in divisional animal shed. *Ad libitum* feed and water were given to animals. All experimental procedures were conducted in accordance with the guidelines approved by the Institutional Animal Ethics Committee (IAEC). Isoprenaline and niclosamide ethanolamine were procured from Sigma Aldrich and Cayman, respectively. Isoprenaline was dissolved in distilled water. Niclosamide ethanolamine was dissolved in DMSO and further diluted in peanut oil.

Experimental animals were randomly divided into four groups namely control (Group I), niclosamide-alone administered group (Group II), isoprenaline-induced cardiac injury group (Group III), and niclosamide-treated cardiac injury group (Group IV). In control group, vehicle was administered for 14 days. Niclosamide ethanolamine was administered at 1 mg/kg body weight (intraperitoneally) on alternate days for initial eight days of experiment in niclosamide alone group. Cardiac injury was induced by administering the isoprenaline at a dose of 20 mg/kg b.w. via subcutaneous route for 14 consecutive days. In treatment group (Group IV), isoprenaline (@ 20 mg/kg body weight) was administered subcutaneously for 14 days, while niclosamide ethanolamine (@ 1mg/kg body weight; I.P.) was given alternatively for initial eight days.

On day 15th of experiment (after 24 hours of the last dose of isoprenaline), the body weights of different groups were measured by weighing balance. Mice were sacrificed then heart was collected and weighed. The tibial lengths of mice were measured by vernier caliper. The relative indices of the morphometric parameters were calculated. Data were statistically analysed using the Graph pad Prism 5 software by One-way ANOVA followed by Tukey's multiple comparison *post hoc* test.

Results

Effect of niclosamide ethanolamine on absolute heart weight in isoprenaline-induced cardiac injury

A significant (p<0.05) increase in absolute heart weight was observed in cardiac injury group (185.0±15.86 mg; n=6) than the control group (125.0±3.41 mg; n=6). Niclosamide co-administration significantly (p<0.01) reduced absolute heart weight (102.8±8.95mg; n=4) compared to the isoprenaline-alone administered group (185.0±15.86 mg; n=6). No significant difference was noted in absolute heart weight in niclosamide-alone (107.0±18.70mg; n=4) and control (125.0±3.41 mg; n=6) groups (Figure 1).

Effect of niclosamide ethanolamine on heart weight to body weight ratio (HWT/BWT) in isoprenaline-induced cardiac injury

No significant difference was observed in HWT/BWT ratio among control (5.65±0.63 mg/gm; n=6), isoprenaline-induced cardiac injury (9.29±1.54 mg/gm; n=6), niclosamide alone (6.20±0.39 mg/gm; n=4) and niclosamide-treated cardiac injury (6.33±0.42 mg/gm; n=4) groups. Although, an increase (non-significant) in HWT/BWT was seen in isoprenaline-induced cardiac injury group (9.29±1.54 mg/gm; n=6) compared to control group (5.65±0.63 mg/gm; n=6) (Figure 2).

Effect of niclosamide ethanolamine on heart weight to tibial length ratio (HWT/TL) in isoprenaline-induced cardiac injury

A significantly (p<0.01) higher HWT/TL was observed in isoprenaline-induced cardiac injury group (9.88±0.97 mg/mm; n=6) compared to control group (6.08±0.29 mg/mm; n=6). Niclosamide-treated cardiac injury group (5.80±0.51 mg/mm; n=4) showed a significantly (p<0.01) lower HWT/TL ratio than ISP-alone administered group (9.88±0.97 mg/mm; n=6). No significant difference was noted in HWT/TL ratio between niclosamide-alone (5.95±0.80 mg/mm; n=4) and control (6.08±0.29 mg/mm; n=6) groups (Figure 3).

Discussions

Sustained activation of sympathetic system is a crucial factor in the advancement of myocardial injury (Tank and Wong, 2015) [14]. The overall functioning of heart is mainly regulated by β-adrenoceptors; therefore, these play crucial role in cardiac disease, especially heart failure (Wachter and Gilbert, 2012) [15]. The morphometric markers like heart weight, heart weight/ body weight ratio and heart weight/tibial length are increased in isoprenaline-induced cardiac injury (Li *et al.*, 2012; Al-rasheed *et al.*, 2015) [16, 17]. Increased heart weight in isoprenaline-induced cardiac injury may be contributed by increased water content, edema of intramuscular space and inflammatory cells infiltration followed by necrosis of cardiomyocytes (Patel *et al.*, 2010) [18]. In the present study, absolute heart weight and heart weight indices *viz*., HWT/TL ratio was significantly higher in cardiac injury caused by isoprenaline which are in accordance with previous studies (Chen *et al.*, 2019; Rana *et al.*, 2023; Sharma *et al.*, 2023) [19, 20, 21]. Niclosamide ethanolamine treatment significantly improved absolute heart weight and heart weight to tibial length ratio in isoprenaline-induced cardiac injury. However, no significant improvement was observed in HWT/BWT ratio in niclosamide-treated group.

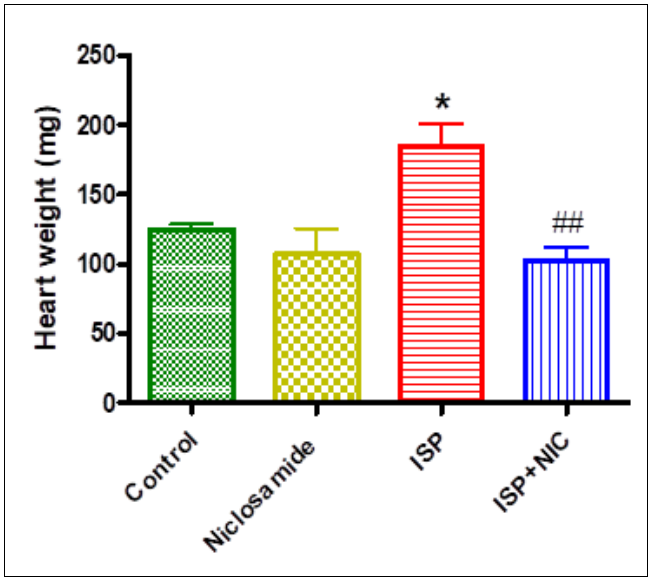

Fig 1: Effect of niclosamide ethanolamine on absolute heart weight in isoprenaline-induced cardiac injury. One-way ANOVA followed by Tukey's multiple comparison *post hoc* test was used. *p<0.05 in comparison to control group; ##p<0.01 in comparison to ISP-alone group.

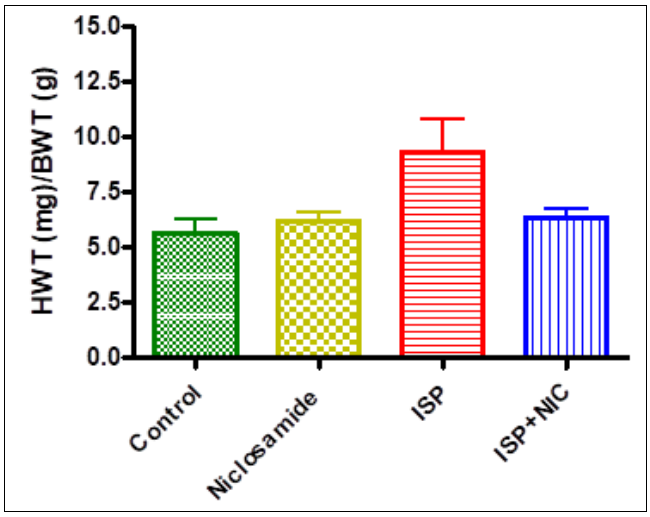

Fig 2: Effect of niclosamide ethanolamine on heart weight to body weight ratio in isoprenaline-induced cardiac injury. One-way ANOVA followed by Tukey's multiple comparison *post hoc* test was used.

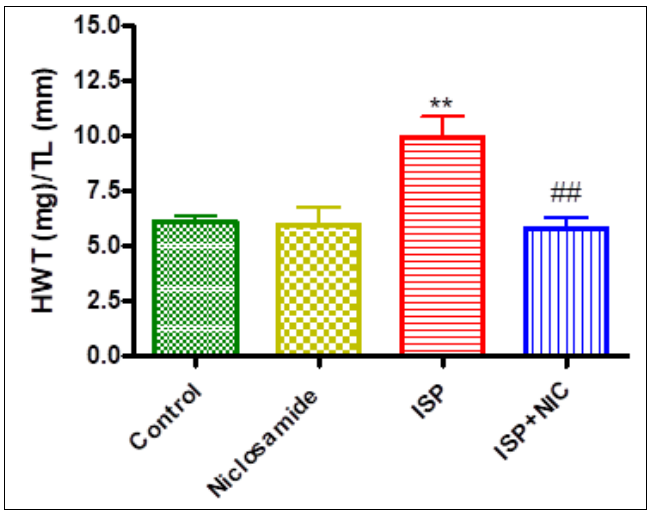

Fig 3: Effect of niclosamide ethanolamine on heart weight to tibial length in isoprenaline-induced cardiac injury. One-way ANOVA followed by Tukey's multiple comparison *post hoc* test was used. $^{**}p<0.01$ in comparison to control group; $^{\#\#}p<0.01$ in comparison to ISP-alone group.

Conclusion

Isoprenaline administration for fourteen consecutive days leads to cardiac injury as evident by increased absolute heart weight and relative indices. Niclosamide treatment decreased the absolute heart weight and HWT/BWT ratio in cardiac injury induced by isoprenaline.

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