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Evaluating the potential Anti-edema effect of Paracetamol on Sprague-Dawley rats

Umar Ibrahim Maryam[1], Nordin Simbak[1], Ibrahim Haruna Sani[1], Atif Amin Baig[2], Umar Faruk Abdullahi [1], Rufa'i Umar Zubair[1], Aliya I.S[1],Thant Zin[2], Swethadri GKM[1], Hadiza Abdullahi Abubakar[3]

[1]Faculty of Medicine, University Sultan Zainal Abidin
[2]Cluster for Biomedical Science, University Sultan Zainal Abidin
[3] Faculty of Health sciences, University Sultan Zainal Abidin

Abstract: **Paracetamol; a drug widely used in management of pain and fever. This research aims to evaluate the Efficacy of paracetamol in the reduction of edema. Croton oil and acetone solution was used to induce the edema. The rats were administered with paracetamol for 21 days after which the croton oil and acetone solution was applied to the inner surface of right ear and same amount of acetone was applied to the left ear while the control group received normal saline also for 21 days. The edema was measured by the difference between the weights of the cut ear tissue which was confirmed by histological analysis. The result showed that there was about 88.46% edema inhibition as compared to the control. Furthermore, the histological findings revealed a significant decrease in edema and inflammation as well as less tissue congestion in the paracetamol group as compared to the control. From this study, paracetomol has shown a promising result in reducing edema and also exhibited some level of ant-inflammatory properties. Thus, this can be helpful in suppressing mild to moderate sub cutaneous tissue edema as well eliciting some ant-inflammatory effect.**

Keywords: **Paracetamol, edema, inflammation, neutrophils, tissues.**

I. INTRODUCTION

Edema is an abnormal swelling caused by accumulated fluid in the tissue. It is the body's response to inflammation (O'Brien *et al.,* 2005), edema can be classified as localized and generalized based on the anatomical parts of the body affected, which can sometimes be life threatening. An aberration in homeostasis of the body fluid generally results in edema. However, a study of the pathophysiology of edema, revealed a number of factors that precipitate the condition. These factors include decrease in plasma oncotic pressure, elevation of net renal filtration, also increase in hydraulic pressure of the capillaries as well as increase permeability (Ros *et al.,* 2004).

Edema in human and animals occurs mostly as a consequence of some underlying problems such as (1) Congestive heart failure: Patients suffering from this condition is at high risk of edema, this occurs due to activation of the rennin angiotensin system which consequently causes vasoconstriction of the renal arterioles (De Bryune, 2003). (2) Lymphedema is a type of edema caused by interstitial fluid elevation (Rockson, 2001), (3) Kidney disease: nephrotic disorders are less commonly associated with edema, but persistence of the condition can causes a severe type of edema, its often accompanied by hyperlipidemia, proteinuria, and hypoalbuminemia (Palmer & Alpern, 1997), (4) Chronic renal insufficiency syndrome: this is a common cause of edema among hypertensive patients (Douglas & Simpson, 1995) (5) Drug-induced edema: Medications such as calcium channel blockers, NSAIDs, estrogens and some vasodilators have been reported to induce edema (Messerli & Grossman, 2002). Edema can also occur as a result of medication failure, a good example is the failure of a loop diuretic such as frusemide to induce a state of negative sodium imbalance (Dormans, *et al.,* 1998).

At present, a number of orthodox medications used in the management of edema include Spironolactone mostly used in conjunction with anti-hypertensive drugs in hypertensive patients (Moore *et al.*, 2003), Frusemide often used as a loop diuretics (Ellison, 1994), Benazapril a potent Angiotensin converting enzyme inhibitor (Pool *et al.*, 2001), certain forms of edema such as ascite and hydrothorax can be treatment via surgical approach known as paracentesis (Salerno *et al.*, 2004). However, these therapeutic approaches are not without some adverse effect which might be severe in some cases.

Paracetamol is an analgesic and antipyretic drug, commonly used worldwide in the management of pain and fever (Hinz *et al.*, 2008). Studies have shown that administration of paracetamol reduces fever and pain without having any adverse effect (Li *et al.*, 2003). Non-steroidal ant-inflammatory drugs (NSAID) and narcotic drugs are the basic drugs used in the management of pain and inflammation, however, despite been therapeutically useful, there application are often associated with series of adverse effects, which ranges from mild to severe complications (Dawood, 1993; Li *et al.*, 2003; Janssen and Genta, 2000; Okafor, 2015; Zipser & Henrich, 1986). This research will help to confirm the anti-inflammatory effect of paracetamol as well as its effectiveness in the reduction of edema. However, this research aims to evaluate the effectiveness of pretreatment of paracetamol in the reduction of edema.

II. MATERIALS AND METHOD

Equipments and chemicals:

LEICA RM 2245 Microtome, LEICA EG 1160 Embedding center, LEICA ASP 3005 Tissue processor, CAT NO 7105 Microscope Slides, cassette box, cassette, hemotoxylin, eosin, scott water, DTX mountant, xylene, acetic acid, formalin,croton oil, acetone, ethanol, xylazin, ketamin, were used for induction of edema and in preparation of histological slides and staining.

Experimental Animals:

Sprague-Dawley, 60 days old rats, were housed six per cage in 2 cages and they were put under controlled condition in photoperiod controlled room (light: dark: 12h: 12h:), humidity (60±5%), temperature (22±2 degrees Celsius), with free access to food and fresh treated water which free from any harmful impurities. All experiments were conducted in accordance with the National institutes of health guideline for the care and use of laboratory animals (NIH Publications No. 80-23) and were approved by the local animal ethical committee (University Sultan Zainal Abidin) with ethic approval letter no (UniSZA.0/3/374-3 (01).

Drug:

Orange flavored children paracetamol suspension (Smithkline Beecham Philippines) was purchased from Baiduri Farmasi, Kuala Terengganu. 60 ml per bottle, each 5 ml containing 250 mg of paracetamol. Making a total of 3000 mg per 60 ml. dose was given according to the weight of the rats (15 mg/kg).

Experimental design:

Twelve Sprague-Dawley rats were randomly assigned into two groups with each group consisting of six rats. Each group of rats was subjected to the following oral treatment daily for 21 days. Group 1 received 15 mg/kg of paracetamol suspension. Group 2 received 0.9% normal saline as control group. On the last day edema was induced using croton oil and acetone solution as follows.

Croton-oil induced ear edema/inflammation:

The inflammation/edema was induced by the application of 5% (v/v) croton oil solution in acetone on the inner surface of the right ears, the same volume of acetone was applied to the left ear (Coruzzi et al., 2012; florentino et al., 2013). Six hours post induction of edema the rat were anesthetized with 5 mg/kg xylazin and 90 mg/kg ketamin, administered subcutaneously (Parasuraman *et al.*, 2010). Ears were excised, 1cm×1cm was cut and the rats were sacrificed by cervical dislocation. The inflammation was measured by the difference between the weights of the cut ears as prescribed by Coruzzi *et al.*, (2012) and Florentino *et al.*, (2013), with little modification and the tissue was immediately fixed in a formalin solution. H&E staining was used for the histological analysis and microscopy was done. Percentage edema inhibition was calculated using the formula.

$$\mathrm{I}\ (\%) = \left[1 - \frac{\Delta W_t}{\Delta W_c}\right] \times 100$$

Where I% = percentage edema inhibition

ΔW_t = change in weight of ear in the treated

ΔW_c = change in weight in ear in the control
(Boukhatem et al., 2014)

Data Analysis:

SPSS software version 20 was used to perform the analysis. Nonparametric analysis was used; Kruskal Wallis one way anova test was used followed by pair wise comparison test. Descriptive statistics of median and inter quartile range was used to describe the variables.

III. RESULT

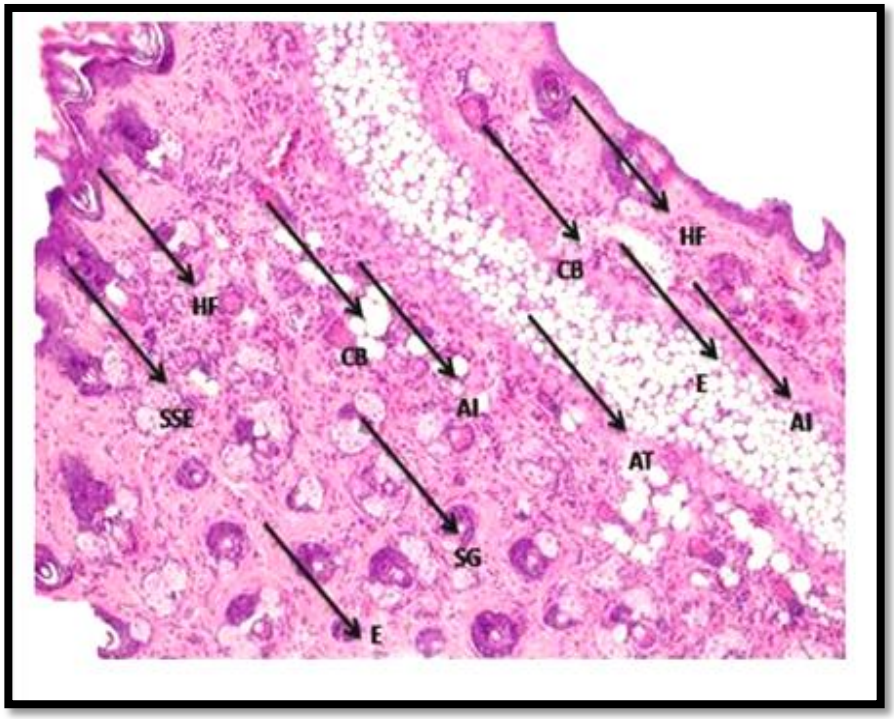
Table 1; Descriptive statistics of median ear weight difference and percentage edema inhibition among the two groups

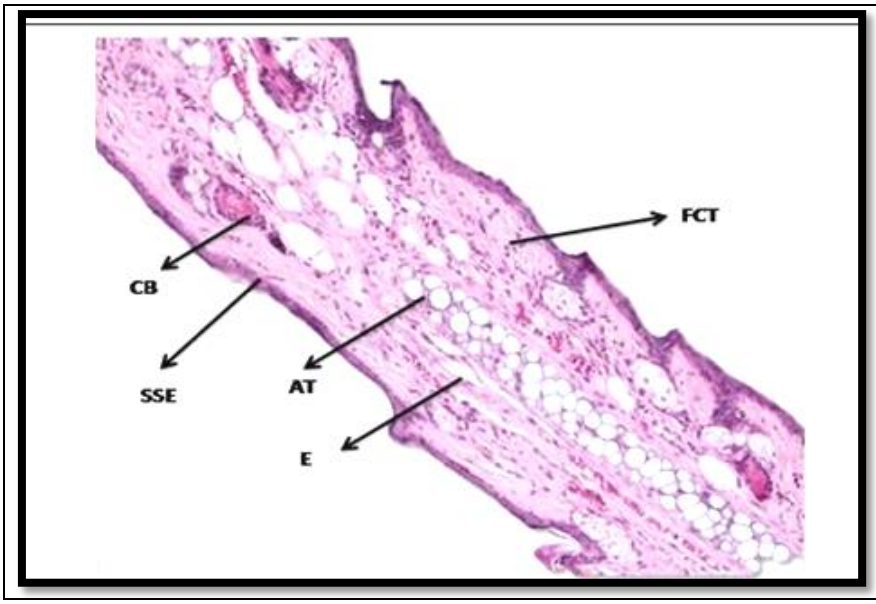
Treatments	Dose	Median (IQR)	% Edema inhibition	χ^2 (df)	p – value*
Normal saline	3ml	0.13(0.19)	--	17.8(3)	<0.001
Paracetamol suspension	15mg/kg	0.015(0.05)	88.46		

*Kruskal-Wallis one way anova. Pair wise comparison test with level of significant set at 0.05, shows that the significant difference lies between group of paracetamol suspension and normal saline (p=0.001)

Table 2 shows that there is less infiltration of neutrophil as well as less edema, apparent sign of inflammation was absent in the tissue, except presence of congested blood vessels. In contrast, there were lots of neutrophilic infiltration observed from the histology of the normal saline treated group, there were also high level of congested blood vessels, more edema and more inflammation as compared to the paracetamol pre-treated.

Table 2; Histological changes on the effect of paracetamol on edema

Groups/Histology slide	Analysis	
Normal saline 	Section shows FCT lined by SSE with areas of edema moderate acute inflammation , infiltration of neutrophiles, with congested blood vessels. Scatered adipose tissue, SG and HF can also be appreciated	SSE- stratified squamous epithelium E-Edema AI- acute inflammation FCT- fibrocollagenous tissue AT-adipose tissue SG- Sebaceous gland CB- congested blood vessels HF Hair folicle
Paracetamol	Section shows FCT lined by SSE	

	with Scattered areas of adipose tisse, congested blood vessels and mild edema in the connective tissue	

IV. DISCUSSION

The primary aim of this study is to investigate the effect of paracetamol involved in its anti-oedemic effect using croton-oil induced oedema inflammatory essay in rats. The data obtained in table 1 shows that paracetamol has the ability to reduce edema induced by croton oil and acetone with 88.5% edema inhibition. This supports the finding of Honore and colleagues as paracetamol reduced the foot swelling caused by carrageen induced oedema (Honore *et al.,* 1995). Although Paracetamol is a weak cycloxygenase inhibitor, its effect in the reduction of swelling after bilateral oral surgery have been recorded (Olstad & Skjelbred, 1986). It was clinically evaluated for its anti-oedematous efficacy which shows that it reduces acute post operative tissue oedema by 30% compared to the placebo (Skoglung et al., 1989).

V. CONCLUSION/RECCOMENDATION

The result showed that paracetamol possesses significant anti-edema and anti-inflammatory properties. Hence, the findings suggest that pre-surgical administration of paracetamol in rats cannot only be an effective means of raising the pain threshold but also will reduce edema and inflammation caused by surgically induced trauma and changes in osmotic gradient of the body. This should perhaps serve as headway towards potential use of parecetomol in human and animal as a pre-surgical medication for the control of edema and inflammation, as well as eliciting its analgesic and antipyretic effect which is known for. To achieve this there will be need for more research to determine the feasibility and safety of this protocol.

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