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Analgesic Activity of Chitosan in Arthritis Rats Induced by Complete Freund's Adjuvant (CFA)

Aktivitas Analgesik Kitosan pada Tikus Arthritis yang Diinduksi *Complete Freund's Adjuvant* (CFA)

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ABSTRACT

Arthritis is inflammation and pain in joints, often accompanied by stiffness and difficulty to move. The current pain treatment in arthritis is synthetic drugs that have many side effects. Chitosan's structure similar to that of glucosamine which can be used as anti-arthritis. This study aims to evaluate the analgesic activity of chitosan in arthritic rats. The heat stimulation method with a hot plate at temperature of 55±1°C was utilized. A total of 25 male Sprague Dawley rats, weighing 150-250 g, were fed and given water ad libitum. There were grouped into group I (normal control), group II (positive control), group III (negative control, given diclofenac sodium), group IV and V (chitosan treatment at 50 and 100 mg/200g BW of rats, respectively). Arthritis in groups II to V rats were induced by subplantar injection of Complete Freund's Adjuvant (CFA) on the first day according to the Anderson method. Analgesic activity was measured every 3 days on day 17 onwards. The obtained data were analyzed using a general linear repeated measure test ($p < 0.05$). The percentage of pain response reduction in normal control, positive control, negative control, chitosan group at 50 and 100 mg/200 g body weight (BW) were 0.30±1.73, -13.46±0.74, 20.37±1.54, 31.52±1.44, and 35.29±0.72%, respectively. Thus, chitosan can be used as an analgesic in arthritic rats.

Keywords: Analgetic, chitosan, diclofenac sodium, hot plate, Sprague Dawley rats.

ABSTRAK

Arthritis adalah peradangan dan nyeri pada persendian, sering kali juga disertai kaku dan kesulitan bergerak. Pengobatan nyeri pada arthritis saat ini masih menggunakan obat sintetik yang memiliki banyak efek samping. Penelitian ini bertujuan untuk melihat

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aktivitas kitosan sebagai analgesik pada tikus arthritis. Kitosan memiliki struktur menyerupai glukosamin yang dapat digunakan sebagai antiarthritis. Metode yang digunakan adalah metode rangsang panas dengan menggunakan hot plate suhu 55±1oC. Sebanyak 25 ekor tikus galur Sprague Dawley jantan, berat 150-250 g, diberi makan dan minum standar ad libitum. Kelompok I (kontrol normal), kelompok II (kontrol positif), Kelompok III (kontrol negatif/natrium diklofenak), kelompok IV dan V (Perlakuan kitosan 50 dan 100mg/200g BB tikus). Sebagai permodelan arthritis tikus pada kelompok II sampai V diinduksi dengan Complete Freund's Adjuvant (CFA) secara subplantar menurut metode Anderson pada hari pertama. Pengukuran aktivitas analgesik dilakukan tiap 3 hari sekali setelah hari ke-17, kemudian dianalisis menggunakan general linear repeated measure test (p<0,05). Hasil penelitian menunjukkan bahwa persentase penurunan respon nyeri dari kontrol normal, kontrol positif, kontrol negatif, kelompok kitosan 50 mg/200 g BB, dan kelompok kitosan 100 mg/200 g masing-masing sebesar 0,30±1,73; -13,46±0,74; 20,37±1,54; 31,52±1,44; dan 35,29±0,72%. Berdasarkan data penelitian disimpulkan bahwa kitosan dapat digunakan sebagai analgesik pada tikus arthritis.

***Kata kunci**: Antinyeri,* hot plate*, kitosan, natrium diklofenak, tikus Sprague Dawley.*

Introduction

Arthritis is a kind of disease characterized by pain, swelling, and muscle stiffness leading to disruption of the function of the moving organs (joints and muscles) (Taylor and Lobo, 2016). It has more than 100 types of diseases, most of which commonly found are artrose (arthritis deformans) generally without inflammation, rheumatism (arthritis rheumatica) with inflammation, spondylosis with inflammation of the spine, reiter syndrome (with inflammation of the kidneys and eye lining), and gout (O'Donnell *et al.*, 2011). Other diseases found include acute rheumatism (septic arthritis) and soft rheumatism, which affects cartilage in other parts of the body (O'Donnell *et al.*, 2015).

Chronic pain is a major health problem in the USA(Dahlhamer, Lucas and Zelaya, 2018). During 2013-2015, 54.4% was suffered from arthritis in the US (Barbour *et al.*, 2017). The prevalence of arthritis in 2010 among adults by sex in 2001 was 37.3% suffered by women and 28.4% suffered by men. In addition, the prevalence of arthritis or CJS based on age was 65 years old and over 58.8%, 45-65 years old 42.1%, and 18-44 years old 19.0% (Cross *et al.*, 2014).

Until now, synthetic drugs are still widely used to treat pain, but they have many side effects, such as disease modifying anti rheumatic drugs (DMARD's), analgesics, and corticosteroids DMARD's is toxic to the kidneys and blood, and diclofenac causes stomach-intestinal complaints (DiPiro, 2008) The toxicity of using methotrexate is gastrointestinal, hematologic, pulmonary, and hepatic. 10% of patients experience diarrhea, nausea, and vomiting. Most of the hematological toxicities are the occurrence of

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thrombocytopenia in 1% to 3% of patients (DiPiro, 2008). National Arthritis Action Plan: a Public Health Strategy (NAAP) emphasizes broad-based efforts to reach that population group. This complementary approach is a traditional medicine model that emphasizes the treatment of individuals suffering from arthritis so that drugs that have the same efficacy as synthetic drugs are sought but have fewer side effects.

Chitosan has a structure similar to that of glucosamine predicted to be anti-rheumatoid arthritis (Bruyere and Reginster, 2007). Kim & Kim (2006) has stated that the inhibitory activity of edema shown by chitosan is caused by the inhibition of the secretion of interleukin-8 (IL-8) and TNF-α from mast cells where both substances are inflammatory mediators. Chitosan also inhibits PGE2 and expression of COX-2 protein as well as pro-inflammatory cytokines such as TNF-α and IL-1. Treatment using chitosan increases the expression of anti-inflammatory cytokines such as IL-10 (Chou, Fu and Shen, 2003). Thus, it is necessary to do research on the success of chitosan therapy as an analgesic for arthritic pain. The method used is the heat stimulation method using a hot plate with a temperature of 55±10^{0}C.

Research Method

Chemical and Reagents

Complete Freund's Adjuvant (CFA) containing *Mycobacterium butyricum* (Merck, London), 50 mg of diclofenac sodium coated tablet (Fahrenheit, Indonesia) obtained from K24 Kusumanegara Yogyakarta pharmacy was as a reference for analgesic drugs (positive control). The carrier material for the test solution used was CMC-Na 0.5%. The test animals used were male Sprague Dawley (SD) rats, 1 month old, 150-250 g of body weight and given AD2 feed and ad-libitum drink obtained from BPOM Jakarta.

The tools used in this study were glassware, such as measuring cups (Pyrex), stir bar, Buchner funnel, spatula and dropper, filter paper, gloves, analytical balance (Sourtorius), thermometer, animal scales (Ohavs), syringe injection (Terumo), oral syringe, and hot plate for analgesic test in test animals.

Methods

1. Preparation of stock suspension solution of 0.5% CMC-Na

   As much as 0.5 gs of CMC-Na was added evenly into a mortar containing 20 mL of hot distilled water then left for 15 minutes until a transparent mass was obtained. After that it was diluted with a water, and put into a 100 mL volumetric flask. Finally it is added with distilled water to mark line.
2. Preparation of diclofenac sodium suspension stock solution

   The suspension of diclofenac sodium used was 0.1% by weighing as much as 0.05 gs of powdered diclofenac sodium that had been mashed, and then it was dissolved

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with 0.5% CMC-Na until homogeneous. Finally, it was put into a 50 mL volumetric flask, sufficiently until marking line with 0.5% CMC-Na suspension.

3. Preparation of 5% chitosan suspension stock solution

   The chitosan suspension used was 5% by weighing 2.5 gs of mashed chitosan, then dissolved with 0.5% CMC-Na until it was homogeneous. It was finally put into a 50 mL volumetric flask until the marking line with 0.5% CMC-Na suspension.

4. Adjuvant-induced arthritic test in rats

   A total of 25 male SD rats were divided into 5 groups (n = 5) and fed and given drink with ad libitum standard. The treatment for each group of adjuvant-induced arthritic test in rats can be seen as follows (1) normal control was given no treatment, (2) negative control was given CFA in day 1 and distilled water in day 17-47, (3) positive control was given CFA in day 1 and diclofenac sodium 1 mg/200 g BW in day 17-47 (4) group IV was given CFA in day 1 and chitosan 50 mg/200 g BW in day 17-47, and (5) group V was given CFA in day 1 and chitosan 100 mg/200 g BW in day 17-47.

   On day 1, rats in the negative control, positive control, and all treatment groups were injected with 0.1 mL of CFA subplantarally in the right palm under anesthesia and then left until the 16th day (Anderson, 1970). After the 17th to the 47th day the rats were treated as described above.

5. Measurement of method analgesic activity (hot plate)

   Changes in pain response of test animals that had been induced by CFA were measured in the form of frequency of hops and hind legs licks for 60 seconds on day 0 as the initial pain response to day 47 using a hot plate device temperature of 55±10^{0}C (Bachhav, Gulecha and Upasani, 2009). Analgesic activity measurement was done when the test animal had arthritis.

Data Analysis

The data obtained from the hot plate method of analgesic power test research was the cumulative pain response frequency in the form of hind legs licking and hopping in each rat in the treatment and control groups for 60 seconds (Bachhav, Gulecha and Upasani, 2009). The presence or absence of analgesic effects can be seen by calculating the percentage reduction in pain response over time as shown in the following formula. The data on the percentage of reduction in mean pain response that had been obtained were then statistically analyzed using SPSS 16.0. Statistical data analysis was performed using a *general linear repeted measure test* with a 95% confidence level ($p < 0.05$).

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Results and Discussion

The analgesic effect of rats with arthritis from chitosan can be seen from the ability to reduce pain response, namely in the form of licking and hopping of hind legs of the rats after being induced with CFA. Rats that had arthritis, both given treatments not, had a different frequency of pain response.

The material in this study was chitosan isolated and synthesized from shrimp shell waste by (Sah Putra & Darmawan, 2015) and (Hanifah & Darmawan, 2015). The deacetylation degree of chitosan obtained was 54.9%. The research conducted by (Hanifah & Darmawan, 2015) found that chitosan at a dose of 100 mg/200 gs of rat's body weight was able to provide a fairly effective anti-inflammatory power, which was 142.66%.

In this study, the tested group consisted of five groups, which were normal control, negative control, positive control with diclofenac sodium as a comparison drug, group ofchitosan dose 50 mg/200 g BW of rats, and group chitosan dose of 100 mg/200 g BW of rats. Each of the group consisted of 6 test animals. On the first day, rats were induced CFA on subplantar as much as 0.1 mL for all groups except normal control.

Observation of the frequency of the pain response was carried out on the 1st day before induction as the initial response, 17th to 47th day done repeatedly every 3 days. This was done to observe significant changes in the frequency of the pain response due to the administration of the test solution or without it. Treatment with the test sample was started on the 17th day after the rat's right leg was checked for arthritis. From the pain response frequency data obtained, it could then be processed to see the percentage reduction in pain response, then compared between the test animals given the test solution and not given it.

The frequency of pain response in the form of hind leg licks and hops increased after CFA injection then the frequency of pain response became less since the first day of drug administration and less based on data collection time after the rats were treated with several drugs with varying doses of chitosan. On the 17th day the intensity of the jump and minute hind licks in the CFA-treated rats became more frequent, proving that there was pain due to arthritis. All CFA treatment groups experiencing a reduction in the frequency of pain response after drug administration can be seen from day 20 to the last day, which was the 47th day. The untreated negative control group of rats showed the largest graph of all the groups. This average pain response can be seen in Table 1.

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Table 1. Frequency of mean pain response in arthritis rats induced Complete Freund's Adjuvant (CFA).

Rat Group	Mean pain response frequency (frequency of jumps and licks/ minute)											
	D-0*	D-17	D-20	D-23	D-26	D-29	D-32	D-35	D-38	D-41	D-44	D-47
Normal control	47.83±0,75	47.33±0,71	47.67±0,76	47.5±0,67	48.50±0,34	47.50±0,42	47.67±0,422	47.83±0,31	46.67±0,42	47.17±0,60	47.00±0,82	47.17±0,93
Negative control	50.00±1,39	68.33±0,99	70.50±0,84	71.67±0,84	72.83±0,79	73.83±0,79	73.50±0,76	74.00±0,73	74.50±1,08	75.67±1,03	76.83±1,06	77.50±1,02
Positive control	46.60±1,07	66.40±0,93	65.60±0,93	64,40±0,75	63.20±0,58	61.80±0,74	60.60±0,55	58.60±0,49	56.60±0,2	55.60±0,55	54.40±0,73	52.60±1.02
Chitosan 50 mg/200 g	43.83±1,49	63.67±1,20	61.83±1,09	60,17±0,95	58.67±1,02	55.83±1,16	53.17±1,01	51.33±1,20	49.17±1,07	47.33±1,60	45.33±1,68	43.67±1,69
Chitosan 100 mg/200 g	50.67±0,95	70.83±1,01	68.00±0,89	65.33±0,80	62.33±0,76	60.67±0,84	58,67±1,05	55.50±1,17	52.50±0,99	50.67±1,05	48.50±0,96	45.83±0,83

Note: * = before induced by CFA

Table 2. Percentage of reduction in mean pain response in rats with arthritis induced by Complete Freund's Adjuvant (CFA)

Rat Group	Mean pain response Reduction (%)											
	D-0*	D-17	D-20	D-23	D-26	D-29	D-32	D-35	D-38	D-41	D-44	D-47
Normal control	0±0	0±0	-0.85±2,50	-0.39±1,01	-2.52±1,29	-0.45±1,51	-0.78±1,16	-1.15±1,21	1.30±1,65	0.30±1,24	0.66±1,57	0.30±1,73
Negative control	0±0	0±0	-3.20±0,62	-4.93±1,21	-6.63±0,96	-8.12±1,41	-7.62±1,19	-8.35±1,00	-9.08±0,82	-10.81±1,04	-12.53±1,23	-13.46±0,74
Positive control	0±0	0±0	1.19±0,72	2.99±0,44	4.81±0,23	6.91±0,52	8.70±0,75	11.70±1,13	14.71±1,08	16.21±1,06	18.02±1,12	20.73±1,54
Chitosan 50 mg/200 g	0±0	0±0	2.87±0,25	5.47±0,61	7.83±0,65	12.31±0,63	16.47±0,78	19.40±0,58	22.78±0,73	25.74±1,22	28.90±1,38	31.52±1,44
Chitosan 100 mg/200 g	0±0	0±0	3.99±0,20	7.75±0,42	11.96±0,90	14.34±0,73	17.20±0,37	21.68±0,72	25.89±0,81	28.48±0,95	31.54±0,73	35.29±0,72

Note: * = before induced by CFA

Table 1 shows that the chitosan dose of 50 mg/200 g BW of rats and 100 mg/200 gs of rat's BW has cut the line of the control group on the 47th and 41st day respectively, which indicates that the chitosan has analgesic properties that can reduce the pain of rats' arthritis back to normal.

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The homogeneity using the Levene's Test on SPSS 16.0 with the repeated measure test method results that all groups, both the control group and the treatment group, are normally distributed (p <0.05). Likewise, the analysis using the between-subject effect test shows that the pain response between groups is significantly different, as indicated by a significance value of 0 (p <0.05).

From the mean pain response frequency data of arthritis rats, the percentage reduction in the average pain response was calculated to see how much reduction in pain response occurred from the treatment group and the control group. The percentage reduction in pain response can be interpreted as how much a substance protects rats from pain due to arthritis. All of the treatment groups were able to protect pain caused by arthritis from day 17 to day 47. Meanwhile, for the negative control group the pain experienced by arthritic rats was increasing day by day due to the absence of treatment in the group rats. Thus, the rats were unable to protect the pain caused by arthritis. In the normal group there was no increase nor decrease in pain response because there was no induction of CFA which resulted in arthritis. The percentage reduction in this pain response can be seen in Table 2.

The results of Levene's Test show the pain mean response reduction percentage data on days 20 to 47, on days 20 and 23 have sig respectively 0.000 and 0.004, which is (p <0.05) that indicates that the data do not come from a normally distributed population. However, analysis using between-subject effect test shows that the percentage reduction in pain response between groups is significantly different, as indicated by a significance value of 0.000 (p <0.05).

The largest reduction percentage in pain response on the last day of data collection, which was the 47th day, was found in the chitosan group 100 mg/200 g BW of rats (35.29%), followed by the chitosan group 50 mg/200 g BW of rats (31.52%). From these results it can be concluded that chitosan at a dose of 100 mg/200 g BW has the greatest analgesic power among all the groups including the diclofenac sodium group (20.73%).

In the within-subject effects analysis, repeated measurements in all groups experienced significant differences, as indicated by the frequency of pain response F(66.340) = 70.42 p <0.05 and the percentage reduction in pain response, the value of F (66.340) = 64.13 p <0.05. Analysis to determine whether there was a relationship between time and differences in treatment in each group was carried out by looking at the results of the between-subject effects analysis. From the results of this statistical analysis, it is known that the frequency of pain response with F (6.34) = 92.07 p = 0.000) and the percentage reduction in pain response (with F (6.34) = 133.34 p = 0.000) can change significantly over time changes.

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Table 3. Reduction percentage in pain response on day 47 after induction of Complete Freund's Adjuvant (CFA)

Rat Group	Pain response reduction (%)±SE
Normal control	0.30±1.73[b,c]
Negative control	-13.46±0.74[a,c]
Positive control	20.73±1.54[a,b]
Chitosan 50 mg/200 g bw	31.52±1.20[a,b,c]
Chitosan 100 mg/200 g bw	35.29±0.72[a,b,c]

Information: a. significantly different from the normal control group ($p < 0.05$), b. significantly different from the negative control group ($p < 0.05$), c. significantly different from the positive control group ($p < 0.05$)

Table 3 shows which groups have a significant difference in ability as an analgesic. The results of the analysis are carried out by looking at the results of the estimated marginal means analysis. The percentage reduction in pain response in the chitosan group 50 mg/200 g BW is significantly different from the percentage reduction in all control and treatment groups. Likewise, the percentage reduction in the pain response of chitosan 100 mg/200 g BW is significantly different from all groups, both control and treatment groups.

The pharmacological mechanism of diclofenac sodium is to inhibit the cyclooxygenase-2 pathway and reduce the production of prostaglandins as a mediator of inflammation (DiPiro, 2008).

The greater percentage of reduction in the pain response of chitosan can happen because chitosan has a similar structure to glucosamine. One of the mechanisms of action of glucosamine is to reduce the production of the COX-2 enzyme so that the expression of IL-1 induced by COX-2 and NF - κB on cartilage explants can be suppressed. In addition, this results in reduced production of PGE2 as an inflammatory mediator and the mediator responsible for chondrocyte cell death (Jerosch, 2011).

Conclusion

To sum up the results of research on the analgesic activity of chitosan in Sprague Dawley rats induced by CFA as a model of arthritis rats, chitosan at 50 mg and 100 mg/200 g of rat body weight can be used as analgesics in CFA-induced arthritic rats with a decreased percentage of pain response 31.29%±1.44, and 35.29%±0.72, and is higher compared to diclofenac sodium (20.73%±1.54).

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