Int J Trans Res Ind Med 2022, 4(1): (P) 33 - 37

Research Article

ISSN 2582-0109

International Journal of Translational Research in Indian Medicine
www.ijtrim.com
Volume 4, Issue 1 – 2022

PRECLINICAL EVALUATION OF ANALGESIC POTENTIAL OF SIDDHA FORMULATION SURINGIYATHI CHOORANAM IN RODENT PAIN MODELS

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ABSTRACT

Sinusitis is accompanied with inflammation of the adjoining nasal mucosa; hence, rhinosinusitis is the recommended word. Inflammation of the nasal mucosa and obstruction of the sinus ostium are crucial factors in the development of sinusitis. Symptoms and indicators of rhinosinusitis include sinus blockage, mucus retention, and infection. The conventional medicine treatment strategy for acute sinusitis emphasizes the use of antibiotics. 85% to 98% of sinusitis patients are prescribed with antibiotics which is of lower therapeutic potential in alleviating the pain and inflammation. Siddha system of medicine continue to be a rich source of structurally novel compounds that may serve as a starting point for the development of novel drugs. The present study aimed at evaluating the analgesic potential of the formulation Suringiyathi Chooranam (SRC) in pain model of rodents. The hot-plate and tail flick method has been found to be suitable for evaluating analgesics with a short acting mechanism of action of analgesic agents. Results of the present study demonstrated that the test drug SRC significantly prolonged the reaction time in the tail-flick method at both the dose levels. Outcomes of the present investigation promises the analgesic potential of the formulation SRC, which would be considered for safe and effective mean of pain management in the conditions like sinusitis in future.

KEY WORDS: ***Sinusitis, Pain management, Prostaglandins, Siddha, Suringiyathi Chooranam, Analgesic, NSAIDs***

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1. Introduction

Sinusitis is a prevalent illness that imposes a substantial financial burden on healthcare systems [1]. Acute sinusitis is the inflammation of one or more paranasal sinuses, with symptoms lasting fewer than eight weeks in adults and less than twelve weeks in children [2]. Sinusitis is one of the top 10 causes for primary care physician visits, and the fifth most prevalent condition for which antibiotics are recommended. In 85 to 98 percent of cases, primary care doctors consider acute sinusitis to be bacterial in origin and give antibiotics. Research clearly demonstrated the efficacy of conventional treatment as adjunctive therapy with an antibiotic for acute and recurrent or exacerbation of chronic sinusitis in children, adolescents, and adults results in facial pain and nasal blockage associated with inflammation.

Analgesics are medications that act on the peripheral or central nervous system to relieve pain selectively without impairing consciousness [3]. Centrally acting analgesics work by increasing the pain threshold and modifying the physiological response to pain. Peripherally acting analgesics, on the other hand, work by inhibiting the generation of impulses at the chemoreceptor site of pain [4]. The animal models used in this study to assess analgesic activity are pain-state models utilizing thermal stimuli such as tail-flick and hot plate methods.

Excitation of nociceptors or their afferent free nerve endings causes pain. There are two types of pain: acute pain and chronic pain, which are mediated by Ad and C fibers, respectively. The mechanism by which noxious peripheral stimuli are transmitted to the central nervous system is called nociception. Nociceptive fibers terminate in the superficial layers of the dorsal horn, where they form synaptic connections with the thalamic transmission neurons. Nociceptors release glutamate, a substance P metabolite that plays a role in neurogenic inflammation [5].

While synthetic anti-inflammatory drugs are currently dominating the market, the possibility of toxicity cannot be ruled out [6]. Numerous drugs have been developed (both nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids), but their safety profiles have revealed that none of them are clearly safe [7]. Due to the adverse effects of synthetic and chemical medicines, namely gastrointestinal irritation and recurrence of symptoms following discontinuation, herbal medicines have made a comeback to meet our basic health needs [8].

Siddha is an old traditional method used to restore an individual's health and well-being. Despite its long herbal pedigree, current technological advancements have explored the real mechanism through which the medication functions. Herbal remedies include physiologically active treatments known as secondary metabolites, which have the ability to prevent the course of a variety of illnesses. Suringiyathi Chooranam (SRC) is a potential siddha formulation listed in the literature for clinical management of several ailments. Hence the present study aimed at evaluating the analgesic potential of the formulation SC in pain model of rodents

2. Materials and Methods

2.1. Animals

Healthy adult Wistar albino rats of either sex weighing between 200-220 g were used for the study. The animals were housed in poly propylene cages and were kept in well ventilated with 100% fresh air by air handling unit. A 12 light / dark cycle were maintained. Room temperature was maintained between 22 ¬+ 2o C and relative humidity 50–65%. They were provided with food (Sai feeds, Bangalore, India) and water ad libitum. All the animals were acclimatized to the laboratory for 7 days prior to the start of the study. The experimental protocol was approved by The Institutional Animal Ethics Committee of Sathyabama Institute of science and technology, Chennai, Tamil Nadu, India. SU/CLATR/IAEC/XVII/181/2021

2.2. Experimental Methodology

The animals were grouped into three groups of 6 animals each. Group I (Control group) -received normal saline, Group II –rats received 250mg/kg of SRC, p.o for the period of 7 days (Day 1 to 8). Group III –rats received 500mg/kg of SRC, p.o for the period of 7 days (Day 1 to 8).On 8th day after drug administration analgesic potential of the formulation have been evaluated.

2.3. Analgesic activity by Hot plate Assay [9]

The eddy’s hot plate assay method will be employed for the purpose of preferential assessment of possible analgesic effects of test drug SRC . Each animal will be individually placed gently on hot plate

at 55oC. Latency to exhibit nociceptive responses such as licking paws or jumping off the hot plate, will be determined 30, 60 and 120 min after administration of the test drug.

2.4. Analgesic activity by Tail-flick method [10]

Anti-nociceptive activity of the test drug SRC will be by the tail-flick method described. About 5 cm from the distal end of the tail of each rat will be immersed in warm water maintained at 50°C. The reaction time (in seconds) will the time taken by the rat to flick its tail due to pain. The first reading was omitted and reaction time was taken as the average of the next two readings. The reaction time will be recorded before (0 min) and at 30, 60 and 120 min after the administration of the treatments

2.5. Statistical Method

The statistical analysis was carried by one-way analysis of variance ANOVA. Results are expressed as ±SEM. The data were statistically analyzed by ONE WAY ANOVA followed by Dunnett's multiple comparison test. Probability P values < 0.05 were considered as significant

3. Results

3.1. Effect of SRC on Eddy's hot plate Method

The hot-plate test is commonly used to assess analgesic potential of the test drug and other siddha formulations. Rats belongs to control group reveals reaction time ranging from 8.8 sec to 9.6 sec in the observed time point. Test drug SRC at both the dose level of 250 mg/kg (8 sec to 11.5 Sec) and 500 mg/kg (8.8 sec to 13.3 Sec) exhibited significant analgesic activity by increasing the reaction time of the rats compared to control group at all observed time points. As shown in Table 1.

Table 1: Effect of SRC on Eddy's hot plate

Group	Before Treatment	After Treatment		
		30 mins	60 mins	120 mins
	Reaction time in Sec	Reaction time in Sec	Reaction time in Sec	Reaction time in Sec
Group I- Control	8.833 ± 0.30	8.5 ± 1.02	8.667 ± 0.71	9.667 ± 0.80
Group II- 250mg/kg SRC	8 ± 0.77	9.667 ± 0.95*	10.5 ± 0.76*	11.5 ± 0.56*
Group III- 500mg/kg SRC	8.833 ± 1.24	11.67 ± 0.84*	12.17 ± 1.4*	13.33 ± 0.66*

Values represent mean ± SEM of 6 experimental animals. * P< 0.05; ** P< 0.01; *** P < 0.001.

3.2. Effect of SRC on Tail flick analgesic activity

Tail-flick response indicates spinally mediated reflex while the paw-licking hot plate response is due to complex supra-spinally integrated behaviour. Findings of the present study demonstrated that the test drug SRC significantly prolonged the reaction time in the tail-flick method at both the dose levels of 250mg/kg (3.3 sec to 8.83 Sec) and 500 mg/kg (2.8 sec to 10.8 Sec). As shown in Table 2.

Table 2: Effect of SRC on Tail flick analgesic activity

Group	Before Treatment	After Treatment		
		30 mins	60 mins	120 mins
	Reaction time in Sec	Reaction time in Sec	Reaction time in Sec	Reaction time in Sec
Group I- Control	3 ± 0.516	3.833 ± 0.54	3.167 ± 0.70	2.333 ± 0.42
Group II- 250mg/kg SRC	3.333 ± 0.49	5 ± 0.57*	7 ± 0.93*	8.833 ± 0.70*
Group III- 500mg/kg SRC	2.833 ± 0.74	5.833 ± 0.83*	8.667 ± 0.55*	10.83 ± 0.60*

Values represent mean ± SEM of 6 experimental animals. * P< 0.05; ** P< 0.01; *** P < 0.001.

4. Discussion

CD4+ T-cells play a vital role in immunological defense by assisting B cells in antibody production, recruiting eosinophils to areas of inflammation, and producing cytokines and chemokines [11]. Th2-type cytokines, including as IL-4, IL-5, IL-13, IL-17, and IL-33, generated by activated CD4+ T-cells augment IgE production and eosinophil build-up [12] and play a pivotal role in the pathophysiology of asthma [13]. Consequently, inhibition of Th2-type cytokine production by activated CD4+ T-cells may prove to be an effective therapeutic strategy for treating inflammatory sinusitis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, acetaminophen, naproxen, and iterocoxib are the most frequently used pharmacotherapies for painful inflammatory conditions. These have been associated with erosive gastritis, peptic ulceration, an increase in bleeding time, a decrease in renal function in renal/cardiac/cirrhotic patients, hyperkalemia, increased risk of stroke, myocardial infarction, and osteoarthritis. [14] Other medications used to treat pain include opioids, which are known for their

sedative, constipating, respiratory depression, tolerance, and dependence-inducing effects. [15]

Herbal preparations exhibit a wide range of biological activity and are thus effectively used to treat ailments [16]. Combining nutritional and therapeutic perspectives might result in a potent weapon for managing a variety of clinical conditions like pain, infection and inflammation [17].The hot plate method, as described by Eddy [18], is the most frequently used thermal nociception model in the evaluation of drugs or compounds' central analgesic efficacy. The hot plate method is a widely used nociception test that utilizes a phasic stimulus of increased intensity [19].

The pain induced by the hot plate's thermal stimulus is unique to centrally mediated nociception . Thus, the prolongation of reaction latency to thermally induced pain in mice using this model suggests antinociceptive activity acting centrally. In the present study rats belong to control group reveals reaction time ranging from 8.8 sec to 9.6 sec in the observed time point. Test drug SRC at both the dose level of 250 mg/kg (8 sec to 11.5 Sec) and 500 mg/kg (8.8 sec to 13.3 Sec) exhibited significant analgesic activity by increasing the reaction time of the rats compared to control group at all observed time points.

Pain is generated in tail flick method via endogenous mediators such as prostaglandins, which stimulate peripheral nociceptive neurons via physical heat. Both narcotics and nonsteroidal anti-inflammatory drugs are toxic to these neuronal fibers. Increased reaction time is widely regarded as a critical parameter of nonselective COX inhibition and nociceptors' central and peripheral analgesic activity [20]. Tail-flick response indicates spinally mediated reflex while the paw-licking hot plate response is due to complex supra-spinally integrated behaviour. Findings of the present study demonstrated that the test drug SRC significantly prolonged the reaction time in the tail-flick method at both the dose levels of 250mg/kg (3.3 sec to 8.83 Sec) and 500 mg/kg (2.8 sec to 10.8 Sec).

5. Conclusion

Inflammation and pain are frequent nonspecific symptoms of a wide variety of diseases including sinusitis. While NSAIDs and opiates have historically been used to treat these conditions, they can cause adverse effects such as gastrointestinal disturbances. Siddha formulations continue to be a rich source of structurally novel compounds that may serve as a starting point for the development of novel drugs. Outcomes of the present investigation promises the analgesic potential of the formulation Suringiyathi Chooranam, which would be considered for safe and effective mean of pain management in the condition like sinusitis in near future

Acknowledgement

I wish to acknowledge my thanks to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India and The Noble research solutions, Chennai, Tamil Nadu, India for their support.

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