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A Comparative Study of Antinociceptive Activity of Fluoxetine with Diclofenac in a Rodent Model

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ABSTRACT:
INTRODUCTION: *Chronic pain affects millions of people, commonly causing depression and anxiety. Antidepressants like fluoxetine have been shown to have analgesic activity with superior safety profile and hence might be better suited in the management of chronic pain.*

OBJECTIVES OF THE STUDY
1) *To evaluate the analgesic activity of fluoxetine.*
2) *To compare the analgesic effect of fluoxetine with diclofenac.*

METHODOLOGY : *Adult albino rats of either sex were used in this study. Screening method used was Eddy's hot plate method.Rats were divided into three groups of 5 animals for above mentioned method and drugs administered as follows:*

Group-1: Distilled water (control)
Group-2: Fluoxetine
Group-3: Diclofenac

Statistical analysis was done by using one way-Analysis of variance (one way ANOVA) followed by Tukey-Kramer test.

RESULTS : *Fluoxetine showed significant analgesic activity in hotplate method, but it was less significant than that of diclofenac.*

Keywords*: Analgesic effect, Fluoxetine, Hot plate method.*

I. INTRODUCTION

Pain is an unpleasant sensation and occurs whenever any tissues are being damaged.Pain has been classified into two major types: fast pain and slow pain. Slow pain also goes by many names, such as slow burning pain and chronic pain. It can occur both in the skin and in almost any deep tissue or organ.Chronic pain afflicts millions of people, commonly associated with depression and anxiety[1]. Currently the most commonly prescribed drugs for management of pain are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like Diclofenac and Opioid analgesics[2].

Some of such conditions causing chronic pain include osteoarthritis, certain cancers or malignancies, migraine headaches, fibromyalgia and diabetic neuropathy.

There are certain areas to which special attention should be paid in the medical history. Because depression is the most common emotional disturbance in patients with chronic pain.[3]

There are various groups of drugs available for management of pain. These include mainly NSAIDs and opioid analgesics. Other adjuvant group of drugs for pain management are antidepressants, anticonvulsants and anti-arrhythmics.NSAIDs are effective for common types of pain and are available without prescription.With chronic use, gastric irritation is a common side effect and is the problem that most frequently limits the dose that can be given. NSAIDs also cause an increase in blood pressure in a significant number of individuals.

Adjuvant analgesics like antidepressants have been useful in specific painful conditions. The selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have fewer and less serious side effects than TCAs, but they are much less effective in relieving pain[4]. The previous studies conducted both on animals and humans to evaluate antinociceptive activity have conflicting results. Hence this present study was carried out with a view to elucidate analgesic activity of fluoxetine, an SSRI and to compare its activity with standard analgesic drugs like diclofenac, a NSAID.

OBJECTIVES

1. To evaluate analgesic activity of fluoxetine
2. To compare analgesic effect of fluoxetine with diclofenac.

II. METHODOLOGY

Materials:

Adult albino rats (weighing: 150-200gms)
Eddy's hot plate
Tuberculin syringe (for injection of drugs)

Drugs: Fluoxetine and Diclofenac were samples from Cipla, Mumbai.

Methodology: The study was carried out at the Department of Pharmacology, M.R.Medical College, Gulbarga on adult albino rats from central animal house of M. R. Medical College after obtaining institution ethics committee approval to undertake this study. Adult albino rats of either sex weighing about 150-200 grams were used for the study, maintained at a temperature of 25±1°C in a well-ventilated animal house and standard laboratory conditions of food and water before start of the experiment. All drugs were administered 30 minutes before the onset of pain stimulus.

Grouping of Animals: Analgesic activity was studied using rats in Eddy's hotplate method[5]observing parameters being the latency of paw licking or jumping. Rats were divided into three groups of 5 animals each (n=5) as follows:

Group 1: Distilled water (control).
Group 2: Fluoxetine (10 mg/kg i.p.)
Group 3: Diclofenac (10 mg/kg i.p.)

Care of the Animals:Handling and care of animals was according to Committee for the purpose of Control & Supervision of Experimental Animals CPCSEA guidelines. Care during the animal study included food, water, shelter etc.

Statistical Methods: The values obtained are expressed as mean±SEM. Statistical analysis of differences between groups was carried out using one-way analysis of variance (ANOVA) followed by Tukey-Kramer test. Probability (P) value of <0.05 was taken as the level of statistical significance.

RESULTS

Table-1: Group-1 – Control (treated with Distilled water)
Latency of response (Paw licking or jumping) in Hotplate Method

Rat No.	Reaction time (seconds)		
	Basal	After 15 min	After 30 min
1.	4	5	6
2.	4	6	4
3	4	3	3
4	5	4	5
5	5	4	4

Table-2: Group-2 (treated with Fluoxetine)

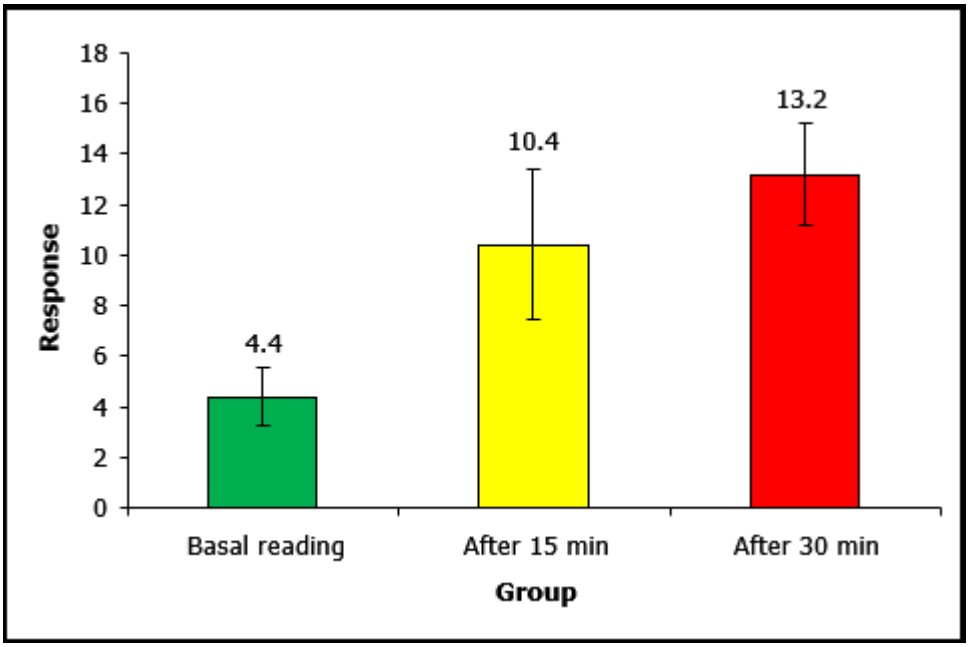
Latency of response (Paw licking or jumping) in Hotplate Method

Rat No.	Reaction time (seconds)		
	Basal	After 15 min	After 30 min
1.	4	7	15
2.	5	10	13
3	3	11	15
4	4	9	10
5	6	15	13

Table-3: Summary Data of Group-2 (treated with Fluoxetine)

Group	No. of Animals	Mean	SD	SEM
A-Basal reaction time	05	4.400	1.140	0.5099
B-After 15 min	05	10.40	2.966	1.3270
C-After 30 min	05	13.20	2.049	0.9165

Figure-1: Comparison of Response (Mean±SEM) in Group-2



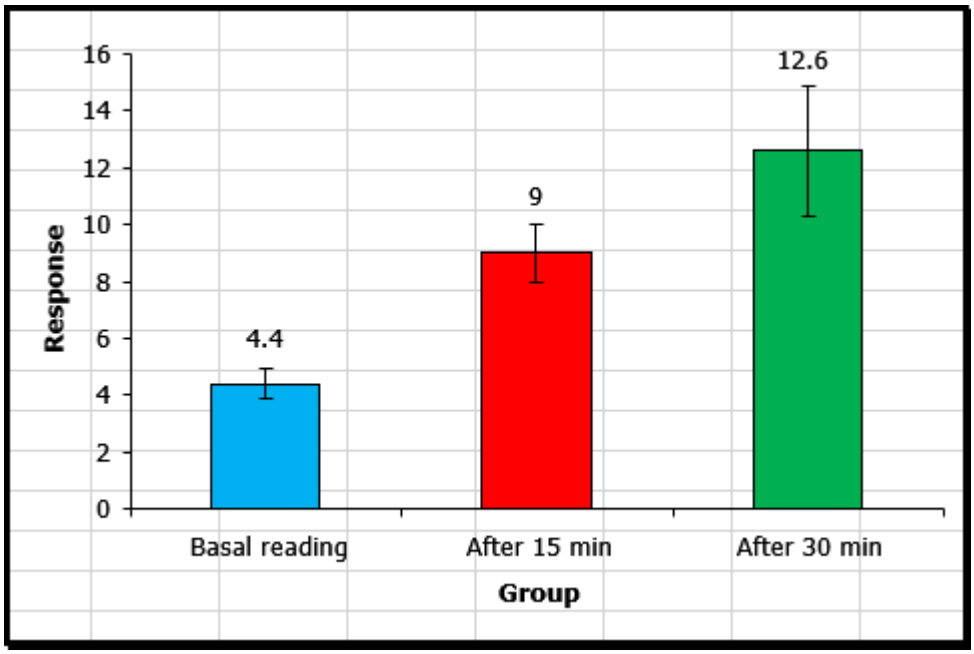
Latency of response (Paw licking or jumping) in Hotplate Method

Rat No.	Reaction time (seconds)		
	Basal	**After 15 min**	**After 30 min**
1.	5	8	10
2.	5	8	12
3	4	9	15
4	4	10	15
5	4	10	11

Table-5: Summary Data of Group-3 (treated with Diclofenac)

Group	No. of Animals	Mean	SD	SEM
A-Basal reaction time	05	4.400	0.5477	0.4449
B-After 15 min	05	9.00	1.00	0.4472
C-After 30 min	05	12.60	2.302	1.030

Figure-2: Comparison of Response (Mean±SEM) in Group-3



ANOVA Results for Hotplate Method:

Tukey-Kramer multiple comparisons test: If the value of q is greater than 3.773, then the p value is less than 0.05.

Table-: ANOVA Results for Fluoxetine

Comparison	q-value	p-value
Basal Vs 15 min	6.145	<0.01
Basal Vs 30 min	9.013	<0.001
15 vs 30 min	2.868	>0.05

Fluoxetine shows significant analgesic activity at both 15 and 30 minutes interval with p-values of <0.01 and <0.001 respectively, but no difference was found in activity at intervals of 15 and 30 mins.

Table-6: ANOVA Results for Diclofenac

Comparison	q-value	p-value
Basal Vs 15 min	6.935	<0.001
Basal Vs 30 min	12.362	<0.001
15 vs 30 min	5.427	<0.01

Diclofenac shows highly significant analgesic activity at both 15 and 30 minutes interval with a p-value of <0.001, but no difference was found in analgesic activity at intervals of 15 and 30 mins.

III DISCUSSION

The study was conducted on three groups of albino rats. Group 1 acted as control not receiving any drug except distilled water. Drugs, fluoxetine and diclofenac were administered to the remaining groups of animals as per protocol. Effect of fluoxetine on nociception was studied and was compared with standard analgesic drug diclofenac. Analgesic activity of fluoxetine has been extensively studied both in animal nociceptive models with mixed results. Hence, the current study was undertaken to evaluate the antinociceptive activity of fluoxetine. The present study showed that fluoxetine demonstrates significant analgesic activity (p-value <0.01 at 15 minutes interval and < 0.001 at 30 minutes interval) in hot plate method.Hotplate analgesic method evaluates only centrally acting analgesics like opioids (e.g., Morphine). Significant activity of fluoxetine in hotplate method points towards mainly central action of fluoxetine. Studies conducted by P.N.Kurlekar and J.D.Bhatt[6] (2004), Schreiber S and Pick CG[7] (2006) and Nayebi A.M. et al[8] (2009), Ada Raphaeli et al[9] (2009) found analgesic activity of fluoxetine to be significant in various analgesic activity screening models. D.Margalit and M. Segal[10] (1979), Mitchell B. Max et al[11] (1992) and J. Sawynok et al[12] (1999) used various analgesic screening models using rodent animals and found fluoxetine lacked significant analgesic activity.

Joseph A. Lieberman[13] (2003) showed through meta-analyses of animal and human experimental trials indicate that antidepressants that increase central levels of both NE and 5-HT, such as dual-acting TCAs like amitriptyline, are more effective in relieving pain than agents with more selective actions on norepinephrine (NE) or 5-HT (e.g., nortriptyline, maprotiline, or SSRIs like fluoxetine and sertraline).

The analgesic activity of standard drug diclofenac was highly significant with p-value <0.001 as expected. The analgesic activity of fluoxetine was significant in hotplate method with p-value of <0.05 in comparison with control but relatively less significant in comparison with diclofenac.

The possible mechanisms of action for analgesia proposed are[14]:

1) Inhibition of GIRK channels
2) Inhibition of serotonin (5-hydroxytryptamine; 5-HT) transporters
3) Inhibition of the functions of 5-HT2C and 5-HT3 receptors
4) Inhibition of nicotinic acetylcholine (Ach) receptors
5) Inhibition of voltage-gated Ca^{2+}, Na^{+} and K^{+} channels and Cl^{-} channels
6) Agonistic action at μ-opioid receptors[15].

III. CONCLUSION

Fluoxetine is an SSRI and one of the most commonly prescribed drug for depression. It is proven to act at multiple sites like serotonin transporter and opioid μ receptor, both of which may play a role in its analgesic activity. Because depression is the most common emotional disturbance in patients with chronic pain, an antidepressant with analgesic activity comparable to TCAs and at the same time with better adverse effect profile will be a welcome discovery. From the present study it is apparent that fluoxetine has significant activity in central analgesic activity model i.e., hotplate method. If proved to be effective from further studies as an effective analgesic, it may be beneficial in patients with chronic pain and associated depression. Fluoxetine showed significant analgesic activity in hotplate method, but it was less significant than that of diclofenac. From the present study, it is difficult to conclude certainly as to whether fluoxetine will be of potential benefit as an analgesic in human beings. Hence further studies need to be conducted to elucidate the significance of antinociceptive activity of fluoxetine.

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