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Research Article

Fluoxetine Outcome for the Treatment of Chronic Low Back Pain: What More We Need to Know

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Abstract

Objective

The purpose of this study was to investigate the possible anti-inflammatory outcome of Fluoxetine, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, in the treatment of patients with chronic low back pain (CLBP).

Methods

Our prospective study investigated 56 patients suffering of low back pain for a period of at least 7 months, who did not need surgical or special medical treatment and did not receive anti-inflammatory medication. Fluoxetine was given daily. Laboratory investigations were performed in three stages: at the beginning, after one month and after three months. The main biomarker of inflammation was C-Reactive Protein (CRP). Data were elaborated using the McNemar's test for high sensitivity C-Reactive Protein (hs-CRP), the paired two-tailed t-test for the other inflammation biomarkers and two-tailed t-test for laboratory investigations.

Results

The number of patients with elevated hs-CRP was significantly decreased (by 16,07%) after the 3-months treatment with Fluoxetine. Body weight index (BWI) was significantly higher in patients with decreased hs-CRP.

Conclusion

Fluoxetine has an anti-inflammatory effect with benefits concerning the feeling of pain in patients with chronic low back pain, expressed as a statistically significant diminution (normalization) of CRP after treatment.

Keywords: Chronic Low Back Pain; Fluoxetine; Body Weight; C-Reactive Protein; Ferritin

Introduction

Antidepressants, tricyclic and selective serotonin reuptake inhibitors (SSRIs), have been used to treat various chronic pain syndromes. Several meta-analyses evaluating the effect of antidepressants versus placebo for short-term therapy (eight weeks or less) in patients with non-specific back pain had conflicting results. Longer-term trials of antidepressants for chronic low back pain are not available [1].

Many patients with pain, as well as patients with psychological and psychiatric disturbances, have elevated biomarkers of inflammation. CRP was found elevated in patients with osteoarthritis of the knee or hip [2]. Proinflammatory activity was also found in patients with depression [3], posttraumatic stress [4], social alienation [5], burnout [6] and other conditions. Proinflammatory biomarkers are also increased in some diseases of the body, such as coronary artery disease, obesity [7] and stroke [8]. This increase is independent of psychological factors.

Recently, discussions about outcomes of antidepressants in patients with chronic pain or psychological disturbances have been launched. CRP was found to be significantly decreased in patients with depression after treatment with SSRIs and thus, it is suggested that antidepressants can have an anti-inflammatory outcome, independent of their antidepressant and neurotropic action [9, 10].

These potential significant therapeutic consequences led us to investigate the outcome of inflammatory biomarkers before and after treatment with SSRIs in patients with low back pain.

Materials and Methods

Study Design

An experimental prospective study between March 2013 and February 2015 was performed on 56 patients suffering of non-specific low back pain for a period of at least 7 months who were treated in the Departments of Neurosurgery, Rheumatology or Anaesthesiology and Pain of KAT National Hospital, mainly as outpatients. After treatment, patients were monitored for a period of at least three months.

In the past, all patients had previously received routine treatment of low back pain, including non-teroidal anti-inflammatory medications but without long-term effect.

The ethics committee of our Hospital approved the design of the study while informed consent was obtained from all patients.

Neuroradiological investigation, including at least a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the lumbar spine had excluded pathology requiring surgical intervention. Rheumatologic or other diseases that would require specialized medical treatment were also excluded on the ground of further investigations performed.

Experimental pain testing was performed at a neutral site (thumbnail) to assess the pressure-pain threshold in all subjects and it revealed hyperalgesia. The pressure required to produce slightly intense pain was 3.9 kg. When pressure was applied, there were detected 5 common regions of neuronal activation in pain-related cortical areas (in the contralateral primary and secondary [S2] somatosensory cortices, inferior, parietal lobule, cerebellum, and ipsilateral S2).

All patients had previously received routine treatment of low back pain, including non-steroidal anti-inflammatory medications, in the past but without long-term effect.

Laboratory investigations were performed in three stages: at the beginning, after one month and after three months. Hs-CRP was chosen as the primary marker of inflammation, but erythrocyte sedimentation rate (ESR), ferritin, fibrinogen and immunoglobulin a1, a2, b and c were also investigated. Simultaneously, patients' history, physical examination - including body height and weight, electrocardiogram, complete blood count, glucose, cholesterol and triglycerides – was investigated by the Laboratories of our Hospital.

Fluoxetine was administered at the standard suggested values of 20 or 40mg/day. It was up to the treating physician to choose the dose based on age and physical condition (reduced dosage for patients with renal or liver dysfunctions).

No anti-inflammatory medications were administered.

Statistical Analysis

Categorical classification has been used for the hs-CRP since each normal value was described as "<0,297mg/dL, normal", without further distinction. Numerical values were given for cases with elevated hs-CRP. Hs-CRP values were consequently considered as normal or elevated.

Following the three-month follow-up, patients were compared to themselves and have been divided into two categories: patients with decreased hs-CRP after treatment (outcome1) and those without (outcome2). We then performed statistical analysis, comparing the same patient before and after treatment, using McNemar's test with Yates correction. Similar statistical analysis with paired t-test was performed for the rest of the inflammation biomarkers. Two-tailed t-test was performed for the laboratory investigations, except for the electrocardiogram, which was grouped as normal or pathological for ischemia and analyzed using X^2 test. BWI was calculated as weight (Kg)/height*height (m^2).

Results

Our study initially included 62 patients. During the follow-up period three patients withdrew the study and other three withdrew medication, mainly because of minor complications, such as dizziness and insomnia. The remaining 56 patients were included in the study. Before treatment 31 (55, 36%) patients had normal baseline hs-CRP and 25 patients had elevated hs-CRP.

Patients with normal hs-CRP were overweight compared to the others. Their BWI was 30,03 compared to 25,54, with a mean difference of 4,49 which is statistically significant at t-test, with P=0,014 and 95% confidence interval of difference 0,97 to 8,01. There was no difference between BWI before and after treatment, with the relevant correlation index being 0,92.

No other statistically significant outcomes were found as far as white blood cells (WBC), glucose, cholesterol, HDL, LDL, triglycerides and electrocardiogram are concerned (Tables 1 and 2).

Table 1. Laboratory investigations. Descriptive statistics.	Outcome	Mean	Std. Deviation	Std. Error Mean
BWI	1	30,0260	5,03008	2,24952
	2	25,5392	3,21906	,63131
WBC	1	6752,50	1871,975	935,988
	2	6783,04	2116,039	441,225
Glucose	1	101,00	5,888	2,944
	2	110,35	47,373	9,878
Cholesterol	1	226,00	30,277	15,138
	2	215,89	52,315	12,002
HDL	1	49,25	6,185	3,092
	2	51,16	13,044	2,992
LDL	1	152,75	32,222	16,111
	2	133,47	35,943	8,246
Triglycerides	1	120,00	20,704	10,352
	2	148,11	106,662	24,470

Outcome1=reduced hs-CRP. Outcome2=not reduced hs-CRP.

Table 1. Laboratory investigations. Descriptive statistics.

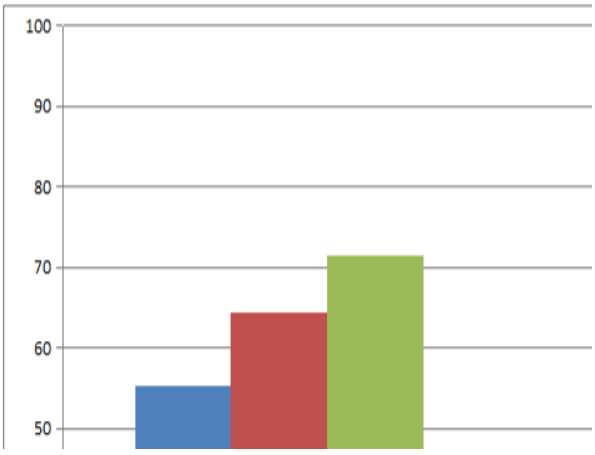
Table 2. Laboratory investigations. T-test.	t	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
					Lower	Upper
BWI	2,607	,014	4,48677	1,72116	,96660	8,00694
WBC	-,027	,979	-30,543	1131,285	-2360,469	2299,382
Glucose	-,388	,701	-9,348	24,100	-58,983	40,287
Cholesterol	,369	,716	10,105	27,378	-46,831	67,042
HDL	-,282	,781	-1,908	6,767	-15,980	12,164
LDL	,989	,334	19,276	19,494	-21,263	59,816
Triglycerides	-,516	,611	-28,105	54,495	-141,433	85,223

Table 2. Laboratory investigations. T-test.

After one-month treatment the proportion of patients with normal hs-CRP increased by 9%. At the three-month follow-up the number of patients with normal hs-CRP increased to 40 (71, 43%) and 16 patients still had elevated baseline hs-CRP (Graphic1).

Graphics

Graphic 1.



crp0= CRP before treatment, crp1= CRP 1 month after treatment, crp3= CRP 3 months after treatment.
0= Normal value (hs-CRP<0,297mg/dL)

	<=0	>0
crp0	55,36	44,64
crp1	64,29	35,71
crp3	71,43	28,57

Using McNemar's statistical test with Yates correction, Fluoxetine resulted in a statistically significant number of patients with reduced (normal) hs-CRP. The X^2 value was 5,82, which is statistically significant.

By using paired two-tailed t-test, there is also no difference in means before and after treatment for ESR, ferritin, fibrinogen, a1, a2, b and c globulins. There is only a tendency towards lower serum ferritin after treatment, which does lead to statistical significance (P=0,109) (Tables 3 and 4).

Table 3. Inflammation biomarkers. Descriptive statistics.		Mean	Std. Deviation	Std. Error Mean
Pair 1	ESR1	21,67	13,178	3,403
	ESR2	19,67	15,296	3,949
Pair 2	Ferritin1	54,4027	36,54927	9,43698
	Ferritin2	46,9740	31,99424	8,26088
Pair 3	Fibrinogen1	4,4569	1,14698	,28675
	Fibrinogen2	4,5669	1,13729	,28432
Pair 4	Globulin a1 1	2,6000	,59020	,16369
	Globulin a1 2	2,8308	,87691	,24321
Pair 5	Globulin a2 1	10,9308	1,53264	,42508
	Globulin a2 2	10,6692	1,48121	,41081
Pair 6	Globulin b 1	12,1308	1,90630	,52871
	Globulin b 2	11,8462	1,55864	,43229
Pair 7	Globulin c 1	13,6154	3,65419	1,01349
	Globulin c 2	14,0308	2,90413	,80546

Table 3. Inflammation biomarkers. Descriptive statistics.

		Table 4. Inflammation biomarkers. Paired t-test.						
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	Sig. (2-tailed)
					Lower	Upper		
Pair 1	ESR1 - ESR2	2,000	10,156	2,622	-3,624	7,624	,763	,458
Pair 2	Ferritin1 - Ferritin2	7,42867	16,83296	4,34625	-1,89312	16,75045	1,709	,109
Pair 3	Fibrinogen1 - Fibrinogen2	-,11000	1,21328	,30332	-,75651	,53651	-,363	,722
Pair 4	Globulin a1 1 - Globulin a1 2	-,23077	,83405	,23132	-,73478	,27324	-,998	,338
Pair 5	Globulin a2 1 - Globulin a2 2	,26154	2,06217	,57194	-,98462	1,50770	,457	,656
Pair 6	Globulin b 1 - Globulin b 2	,28462	1,93600	,53695	-,88529	1,45453	,530	,606
Pair 7	Globulin c 1 - Globulin c 2	-,41538	1,74969	,48528	-1,47271	,64194	-,856	,409

Table 4. Inflammation biomarkers. Paired t-test.

Discussion

Although elevated inflammatory biomarkers are classically associated with infectious or inflammatory human diseases, these biomarkers have been found to be elevated in many other important conditions [i.e. coronary artery disease, obesity, stroke, depression, etc.]. Literature has also revealed that the correlation between depression and elevated biomarkers is independent of other factors, such as age, overweighting, cholesterol, triglycerides, and heart diseases [11]. Others have found only a weak correlation, which vanishes after correction for body weight [12].

Experimental works suggest that Fluoxetine - along with other antidepressants - can have an anti-inflammatory effect, independent of its antidepressant and neurotropic action [13-15]. The mechanism of action is thought to be inhibition of nitric oxide, prostaglandin E2 and hyaluronic acid in human synovial cells [16] or induction of pituitary-adrenocortical activation via serotonin [17]. This action can improve pain [18]. Other studies revealed that exercise could also reduce CRP in patients with low back pain [19].

Since SSRIs are often used in the treatment of chronic spinal pain, we decided to prospectively study patients with chronic low back pain for the possible anti-inflammatory effect of Fluoxetine, a known SSRI.

There are few previous similar studies of patients with acute or chronic low back pain or sciatica, which gave negative results, by comparing healthy subjects with the above described patients, but not comparing the same patient before and after treatment with SSRI [20]. We have consequently compared each patient before and after treatment, using the appropriate statistical tests. Neuroradiological investigations and neurosurgical consultation had precluded neurosurgical emergencies or conditions such as active osteochondrosis, disc or facet joint degeneration as underlying pathoanatomic correlate for CLBP.

Several studies emphasize the existence of patients who can have atypical rheumatologic diseases that could not be excluded from research samples (i.e. patients with fibromyalgia without the necessary 11/18 trigger points) [21]. However, there is no evidence that the results of our study have been affected by such cases since rheumatologic consultation had also excluded rheumatologic diseases, which would need special treatment, including fibromyalgia and polymyalgia rheumatica. This led to a more homogeneous population, because rheumatologic diseases might have had spontaneous aggravations or remissions, which could have confounded the outcomes. CRP was chosen as the main inflammation marker, because previous relevant literature has shown it to be the most sensitive and specific marker. Subsequently, our analysis revealed that Hs-CRP was indeed statistically significantly reduced (normalized) after treatment (by 16,07%).

In conclusion, our experimental prospective study on 56 patients suffering of low back pain revealed that administration of Fluoxetine at the standard suggested values of 20 or 40mg/day has a significantly positive outcome with benefits concerning the feeling of pain. Precisely, treatment with Fluoxetine has an anti-inflammatory effect in patients with chronic low back pain, expressed as a statistically significant diminution (normalization) of CRP after treatment. However, our study has several limitations and further research is necessary in order to generalize this statement. The number of patients with initially elevated CRP, who went back to normal after treatment, is small. We did not randomize and compare untreated to treated patients. That means that data presented are not sufficient to generalize the statement that Fluoxetine has an anti-inflammatory effect on patients with chronic low back pain. Last but not least, more research needs to be carried out in order to assess the exact clinical benefits of CRP diminution on patients with chronic low back pain.

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