Does Diclofenac improve cognition and daily living functioning in Parkinson patients?

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Abstract—Recent studies showed nonsteroidal anti-inflammatory drugs (NSAID's) may play a role in reducing the incidence of neurodegenerative diseases especially Alzheimer by inhibiting brain COX isoenzymes. We aimed to evaluate the effect of the non selective COX inhibitor drug diclofenac on the cognition associated with impaired daily functioning in Parkinson's disease patients (PDP). A single-blind, randomized clinical trial conducted in two groups of 20 parkinsons patients, treated group (n=10) were given 100 mg diclofenac twice daily with omeprazole for 2 months. The cognition was measured by MMSE and MoCA test and daily living function was assessed by ADCS-ADL scale. The outcomes were better among patients treated with diclofenac than among those who were control patients. Diclofenac treated patients showed significant improvement (P< 0.001) in MMSE & MoCA scores after 2 month treatment period from baseline score of (P = 0.79 & P = 0.64). Clinically improved scores were observed in the ADCS-ADL scale after 2 month treatment of diclofenac as compare to control group (P<0.001). Significant better results were observed after 2 months treatment with diclofenac with respect to disease severity (UPDRS III score & Hoehn and Yahr stages). The most frequent adverse event during 2 month treatment period were nausea, dyspepsia, elevated hepatic transaminases, hypertension and increased urea, creatinin levels.

In conclusion results of this randomized trial explain that diclofenac administration shows moderate improvements in PD associated cognitive decline and their daily life function but adverse drug events were also observed. Hence prolong use of diclofenac cannot be recommended to treat PD associated dementia.

Index Terms— Diclofenac, Parkinson's disease patients (PDP), Minimental state examination (MMSE), Montreal cognitive assessment test (MoCA), the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) scale

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1. Introduction

Parkinsons disease (PD) is one of the common type of neurodegenerative disorder caused when dopaminergic neurons and nerve terminals that control body movement lose their activity and die [1]. The neurodegeneration of Parkinson's disease was considered previously as just neuronal damage, but recent researchers indicate that other pathogenic factors are involved in PD progression [2]. More specifically inflammatory mediators, especially over expression of COX 2 and PG E2 levels in the mid brain region and substantia nigra are associated with PD [3]. Several human and animal studies proposed the key role of COX2 in microglial activation and toxic free radicals production in the PD pathogenesis [4, 5]. On the other hand COX1 is mostly concentrated in microglia and could be responsible for glial cell inflammation [6]. Over expression of COX1 at beta myeloid plaques is liable for memory deficit in Alzheimer's and Parkinson's patients [7, 8], Several epidemiological and experimental studies demonstrated that long term use of NSAID's may reduce Alzheimer's risk and improves dementia by reducing brain inflammation [9, 10]. Different NSAID's are being investigated as Alzheimer and PD protective agents including ibuprofen, naproxen, indomethacin, meclofenamates and aspirin [11]. Experimental and clinical studies suggested NSAID's may improve PD associated dementia NSAID's reduces the generation of free radicals from activated microglial cells and reduces beta amyloid induced neuroinflammation which improves memory [12, 13].

Recent studies shows that NSAID's like diclofenac improves neuroinflammation induced by microglial and astrocytic activation, act as agonist for peroxisome proliferators activated receptor gamma(PPARɣ) [14, 15] and may be used for treating Alzheimer and PD disease associated learning and memory deficit [16]. In 2011 Gao X. and Honglei C. et al [17] conducted a study indicated that patients who receives regular use of NSAID's had a lower risk of PD then non regular users. Furthermore Glenda M. et al [18] conducted a case control study and concluded long term NSAID's use in patient with Alzheimer disease enhanced cognitive performance but did not alleviate the progression of disease. On the other hand further epidemiological studies suggest that long term use of

NSAID's may show protection from PD and Alzheimer disease progression & mild cognitive decline [19, 20, 21]. Thus after strong in vivo and biochemical rationale there is a need to test the effective role of NSAID's especially diclofenac in Parkinson patient's clinical trials.

This study was conducted to assess and clarify the possible CNS effects of diclofenac sodium in parkinsons patients to improve their sign and symptoms of disease progression and on their memory and life style.

2. Methodology

We performed a single-blind, randomized clinical research, our recruitment period was 16 month during that period we recruited 25 pateints who were screened in out patient department of Neurology of Abbasi Shaheed Hospital Karachi Pakistan. 20 of these patients agreed to participate while 2 patients refused to participate and not given written informed consent and 3 others did not meet our study criteria. All recruited patients ages were between 45-80 years, they could speak and write Urdu fluently and they were taking L-dopa only to avoid any neuropsychiatric effect of other anti-Parkinson's drug. The United Kingdom Parkinson's Disease Society Brain Bank criteria was used to diagnose Parkinson's disease. After diagnosis all patients baseline clinical profile like liver, hepatic and blood cells counts were measured and patients were divided in 2 groups A & B. Group A, n=10 was control and group B, n=10 was diclofenac treated group. Our follow up period was of 2 months after every one month all investigational tests have conducted to assess cognition and daily life activity and blood chemistry profiles were carried out to rule out the NSAID's toxicity. Exclusion criteria included the presence of any neurodegenerative disease other than Parkinson's disease or other reason of cognitive decline, medication interfering with cognition (i.e. Hypnotics or tranquilizers), deep brain stimulation, Subjects with peptic ulcer, renal, hepatic problem & allergy/sensitivity to diclofenac drug or its excipients, the presence of any disease or debility distinct to Parkinson's disease and the use of a cholinesterase inhibitor or Para sympatholytic drugs during the one month before inclusion in the research.

The study was approved by the Karachi medical dental college ethical review board, Reference # CHS. 097/11, all PD patients or their informants filled informed consent form before study started. All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the declaration of Helsinki 2004.

2.1 Medication

Group B received diclofenac sodium100 mg orally with omeprazole, twice daily during a period of 2 months, and the other group A patients received only their normal medication other than diclofenac, during 2 months follow up period.

2.2 Outcomes

Efficacy assessments of diclofenac sodium on disease severity, cognition and Parkinson patients daily life activity were made at baseline, after 1 month, and after 2 months. The cognitive decline was diagnosed by the neurologist for each PD patient by applying the Diagnostic and Statistical manual Mental disorder IV (code 294.1) further MMSE [22] and MoCA [23] were administered by trained staff. The MMSE is a common cognitive test used to assess orientation, verbal memory, language, attention, and visuo-constructive abilities. however some studies have challenged MMSE efficacy as a screening instrument in Parkinson's disease, because it lacks specific tests for executive function assessment [24, 25], that's why MoCA test also being used to find more accurately cognitive decline in Parkinson's patients. To identify mild to moderate cognitive decline in PD patients, we first identified all patients who had a MMSE score<26 and MoCA score <26 and declared them cognitively impaired Parkinson's patients and Parkinson's patients who had MMSE & MoCA score>26 were considered as cognitively unimpaired.

After cognitive status determination of each patient then different visit was scheduled to evaluate the daily living performances in PDP "The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) scale" was administered by independent rater [26]. For this purpose interviews were conducted with patient's informant before study started and after 1 and 2 month respectively, In our study most of the informants were their spouse, son or any relative who lives in their home. We asked the informant about the patient and filled out the ADCS-ADL scale according to the patient's observed action and behavior, for which scores can range from 0-78 points, with lower scores indicating poor performance [27].

Safety evaluations of diclofenac included recording all adverse events, results of laboratory tests, vital signs, and body weight. Adverse Changes in symptoms of parkinsonism were assessed at baseline and at after 1, and 2 month period by means of the motor-examination section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS), maximum score = 108 higher score means worst motor symptoms [28] and further motor examination assessed by Hoehn and Yahr staging [29]. These examinations were carried out by movement disorder specialists.

3. Data Analysis

The data were analyzed by using SPSS version 21.0 for Windows. Comparisons of demographic and clinical characteristics between control and treated samples were performed using Independent sample t-test and univariant analysis. Comparison of cognitive tests MMSE & MoCA and daily living functioning (ADCS-ADL scale) from baseline, after 1 month and 2 month were measured by multivariate analysis. PD Disease severity among both control and treated groups during 2 month treatment period were compared by multivariate analysis. The treatment related adverse events were compared with control group by chi square statistics, with p-value less than 0.05 is considered significant.

4. RESULTS

4.1 Baseline Patient's clinical and demographical characteristics

A total of 20 patients completed all study assessment procedure. The baseline demographical and background characteristics of the sample population are listed below in table 1.

Table 1. Shows there were no statistically significant differences between control and diclofenac treated Parkinson patients, with regard to gender distribution, age, weight, total daily levo dopa dosage, Hoehn and Yahr staging and UPDRS scores, MMSE , MoCA and ADCS-ADL scores.

Table: 1. Baseline Patient's clinical and demographical characteristics

Variables	control n=10	diclofenac treated n=10	P value
Age	63.6±9.08	64.21±6.37	0.91
L dose	477.5±205.7	593.5±207.6	0.22
disease duration	4.23±1.23	4.07±1.74	0.815
UPDRS III	29.9±4.95	28.8±4.96	0.626
H & Y stages	2.0±0.667	2.1±0.843	0.772
MMSE	20.5±2.54	19.7±2.51	0.793
MoCA	19.5±4.01	18.62±3.42	0.64
ADL	44.80±5.3	44.40±6.05	0.877

Values are mean + S.D. (n=10). Significant differences by Newman-Keuls test *p<0.05, **p<0.01, as compared to control group, following data analyzed by Univariate analysis df (1,18).

4.2 Assessment of memory and daily living performances of diclofenac treated patients compared to control group after 1 and 2 month follow-up.

As compared with the patients in the control group diclofenac receiving patients had insignificant results after 1 month but showed improved significant MMSE and MoCA scores after 2 month of treatment (P<0.001) which shows improvement in memory impairment after 2 months diclofenac treatment. Also diclofenac treated group showed significant scores after 2 month of treatment in ACDS-ADL scale (P<0.001).

Table: 2. Assesment of memory and daily living performances of diclofenac treated patients compared to control group after 1 and 2 month follow-up.

| variables	control group n=10			diclofenac group n=10			P value
	baseline	after 1 month	after 2 month	baseline	after 1 month	after 2 month	
MMSE	20.5±2.54	20.76±2.61	19.3±2.45	19.7±2.51	20.01±2.52	23.75±3.16*	< 0.05
MoCA	19.5±4.01	19.81±4.06	19.45±4.01	18.62±3.42	19.11±2.48	21.45±4.65*	< 0.05
ADL	44.90±5.44	44.65±5.86	43.25±5.32	44.90±5.3	44.92±5.34	45.85±5.86*	< 0.05

Values are mean + S.D. (n=10). Significant differences by Newman-Keuls test *p<0.05, as compared to control group, following data analyzed by multivariate analysis df (1,18).

4.3 Assessment of Parkinson's disease severity of diclofenac treated group compared to control group between 2 month follow up.

Figure 1a and 1b showed Parkinson's disease severity by UPDRS III and Hoehn and Yahr staging. Fig 1a explain diclofenac treated group showed significant decreased

scores of UPDRS III after 2 month treatment of diclofenac (P<0.05) as compare to control group.

Figure 1a and 1b: Parkinson's disease severity of diclofenac treated group compared to control group between 2 month follow up.
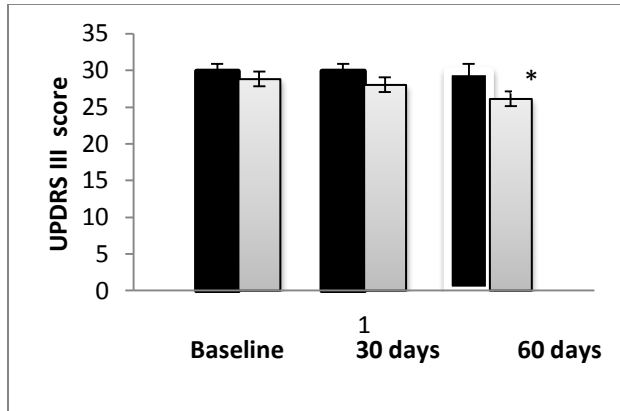
*P<0.05   **Fig 1a.**

Fig 1b shows disease severaity by Hoen and yahr stages there were no change seen in both control and diclofenac treated groups after 1 and 2 month research period. Insignificant differences shows diclofenac does
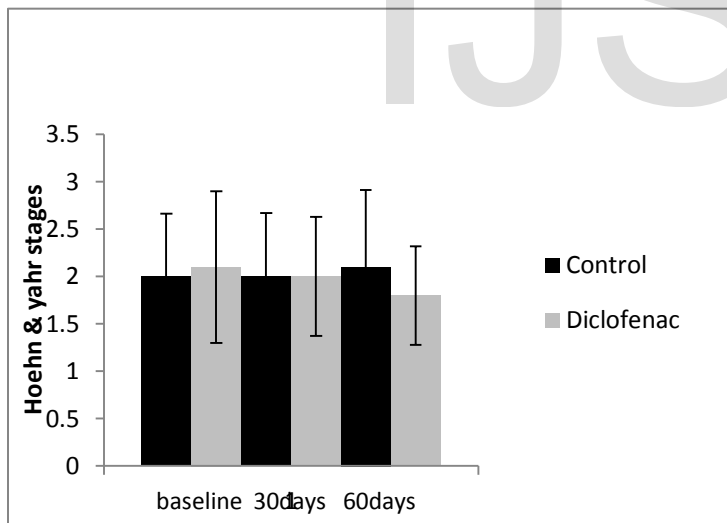not have impact on Heohn and Yahr staging.

Fig 1b.

4.4 Most frequently reported treatment related adverse drug events during 2 month treatment period of diclofenac sodium

The diclofenac treated group patients had adverse drug events especially marked or moderate worsening was seen after 2 month of treatment. The most common adverse drug events were gastrointestinal related like dyspepsia, nausea

and diarrhea etc. out of 10 patients 2 (20%) patients complain of hypertension, 3 (30%) patients had increased urea & creatinin levels, hepatic transaminases AST & ALT levels were significantly increased in 3 (30%) patients after 2 month treatment of diclofenac sodium. Also 2 (20%) patients complain of skin rash after 2 month of treatment period.

Table: 3. Most frequently reported treatment related adverse drug events during 2 month treatment period of diclofenac sodium

adverse events	baseline	after 1 month	after 2 months
GI			
Dyspepsia	-	1(10)	3(30)
epigestric pain	-	-	2(20)
nausea & vomiting	-	1(10)	3(30)
loss of appetite	-	1(10)	2(20)
Diarrhea	-	1(10)	3(30)
Renal			
peripheral edema	-	1(10)	2(20)
Hypertension	-	1(10)	2(20)
increased creatinin	-	1(10)	3(30)
Hepatic			
elevated ALT	-	1(10)	3(30)
elevated AST	-	1(10)	3(30)
Skin rash	-	-	2(20)

5. Discussion

Our result indicates that diclofenac which is non selective COX inhibitor improved memory and daily life

performances among patients with dementia associated with Parkinson's disease, indicating that diclofenac may have a role in restoring memory function. This result is consistent with a recent study which explains diclofenac improves scopolamine induced memory dysfunction in rats [29]. Cognitive decline associated with PD is due to the over expression of COX isozymes, previously it was known that dementia in PD was due to cholinergic deficit [30] but recent researches indicate that not only cholinergic but over expression of both (COX-1 and COX-2) isoenzymes in

hippocampus and cerebral cortex leads to impair memory consolidation [31, 32, 33] COX-1 and COX-2 both contributes significant mediation of PGE2 response at synapse which is responsible for dopaminergic neuronal degeneration [34, 35] and suppression of long term memory potenciation [36]. Thus inhibition of PGE2 receptor by NSAID administration may have beneficial role [37, 38].

To our knowledge this is a first reported clinical study to investigate the role of diclofenac in PD patients. Previous studies [39, 40, 41] investigated the role of ibuprofen and aspirin in parkinsons and its associated dementia. In our study we found MMSE and MoCA scores significantly increased from baseline (P<0.05) after 2 month treatment of diclofenac as compare to control group. Most patients in the diclofenac group than in the control group had an improvement in the ACDS-ADL score (P<0.01), this result is in accordance with previous studies which indicated that daily living functioning depends on cognition [40] and NSAID's have positive impact on PD associated cognitive impairment [42].

In our study pateints in the control group and diclofenac treated group both didn't show any change in Hoehn & yahr staging (P>0.05) whereas UPDRS III motor score in diclofenac treated group were slightly decreased but difference in the rate of improvement were small. This result outcome suggest diclofenac treated patients did not show clinically meaningful improvements in disease severity except in memory improvements. This may be due to the fact that inhibition of COX isozymes in neuroinflammation is dose and time dependent. Our study period was 2 month which is a short period, future studies in large cohort with long duration of treatment and high dose may give better results on disease progression and severity.

NSAID's associated adverse events profile in Parkinson patients were due to prostaglandins inhibition in GI, renal system and its toxic metabolite accumulation in liver [43, 44]. the most common adverse event were dyspepsia, nausea and slightly elevated hepatic transaminases (30%) and creatinin levels (30%). 20% patients showed increased blood pressure after 2 month treatment, increase blood pressure was highly associated with history of hypertension. However elderly PD patient should be carefully monitored when using diclofenac. this finding is consistent with previous study that showed that diclofenac can increase systolic blood pressure [45].

6. Conclusion

In conclusion our study confirms that diclofenac significantly improve memory and daily functioning of PD patients but not disease severity. Our results suggest that there is a need to conduct trails on large PD cohort for longer duration of therapy to predict clinically meaningful response of diclofenac on cognition.

7. Aknowledgment

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