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Original Research Article

Evaluation of C-reactive protein and magnesium level in migraine patients on pre and post prophylactic treatment

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ABSTRACT

Migraine affects the day to day life of the sufferers with the symptoms of photophobia and phonophobia with pulsatile or non-pulsatile headache lasting from 1 to 4 hours. Prophylactic treatment or anti-migraine drugs were given to migraineurs to overcome the complications. C-reactive protein (CRP) and Magnesium level of symptomatic migraineurs, which act as biomarkers for the inflammatory cerebrovascular diseases before and after the treatment with Sodium Divalproex, Flunarizine and Propranolol. The evaluation of C-reactive protein and magnesium levels are noted along with symptoms when they first walk into the clinic. Treatment provided with Sodium Divalproex, Flunarizine and Propranolol for one month. After 1 month, the same tests are being performed. During the test at first instance, the values of pain scale were 31%, CRP value for negative were 20% and positive were 80% and pre-test of Serum magnesium level was 8.8% and at the second visit the pain scale reduced to 10.25%; CRP level was negative 25% and positive was 75%; Serum Magnesium was 9.35%. So, the significant values are being measured by the statistics, which we applied and found P=0.05. The patients who visited first didn't come for the second visit. So, the results might vary and the patients who visited for the second time after one-month treatment, some got effective results while others remained ineffective. The reason for being ineffective is that they might have adapted to their current regimen.

1. Introduction

Migraine is a neurological syndrome which is associated with unilateral or bilateral, pulsatile or non-pulsatile headache accompanied by photophobia, phonophobia with nausea and vomiting.[1–3] The prevalence of this disease in women is greater than in men. ICHD (international classification of headache disorder) classified migraines into different types and the most common types are: Transformed migraine, Migraine with aura, Migraine without aura and Chronic migraine. The hypothesis given by Wolff's proposed migraine as vasospastic disorder.[4] In the early vasoconstrictive stage, meningeal blood vessels dilate, activating the trigeminal sensory nerve which surrounds them triggering pain. The activation of trigeminal nerves also causes the release of vasoactive neuropeptides that further contribute to dilation, neurogenic inflammation of pain-sensitive cranial structure and worsen the pain.[5] The activation of trigeminal nerve branches, cerebral vasodilation of brain nerves following nerve stimulation resulting from pain, can be one of the causes of the inflammatory process of migraine headache. Vasodilators in cerebral nerves include Vasoactive Intestinal Peptide (VIP), Peptide Histidine Isoleucine (PHI), Neuropeptide Y (Nry), Substance P (sp) and Calcitonin Gene Related Peptide (CGRP).[6]

C-reactive protein (CRP) is synthesized by the liver,[7] which is transported into the bloodstream in

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response to inflammation. Inflammation within certain brain tissues resulting from neuronal activation and the subsequent release of pro-inflammatory neuropeptides from perivascular nerve endings is supposed to occur during migraine attack.[8] The inflammation of extra- parenchymal vessels mediated by trigeminal peptide release.[9–11] The inflammation can be noted by imaging but the relation of CRP elevation to potential ischemic or white matter changes remains unknown.[12] The CRP level was evaluated with a blood test and the cause or location of the inflammation might not be specific. Also, studies proved that CRP level is increased in migraineurs.[13–15]

Recent research on Serum Mg levels shows that over 50% of patient's Serum Mg level has been decreased during migraine attacks. Reduction in the magnesium level can lead to opening of calcium channels which will increase intracellular calcium and then eventually the release of glutamate and increased extracellular potassium, which causes brain depression in migraine.[16]

A wide variety of factors has been suggested for increased irritability, including low magnesium level of the brain, mitochondrial abnormalities and dysfunction related to increasing nitric oxide or calcium channels.[17,18] Magnesium deficiency can be associated with stimulation of excitatory neurotransmitters such as acetylcholine and serotonin.[19] Migraine can be primary or secondary to low intracellular free magnesium because of systemic free magnesiumion deficiency. Few studies suggest low serum magnesium levels in migraine patients.[20–22]

The prophylaxis treatment of migraine includes Divalproex Sodium, Flunarizine and Propranolol. Flunarizine is a calcium channel blocker, which has H1 blocking activity that reduces smooth muscle spasm and has consistently shown efficacy in many trials.[23,24] Propranolol is a beta-blocker which has gold standard prophylaxis for migraine.

Valproic acid is an anticonvulsant drug shown to reduce migraine attack frequency in several placebo-controlled trials. Valproate has the experimental evidence that it suppresses neurogenic inflammation and directly attenuates nociceptive neurotransmission. Recently, a study shows that valproic acid enhances the responsiveness of GABA-A receptors by interaction with at least one of the receptor modulation sites.[25] Valproic acid elevates GABA by inhibiting GABA transaminase, the enzyme responsible for GABA degradation.[26]

2. Materials and Methods

We have conducted the study at Vinayaka Neuro Multispeciality Centre by following ethical standards with acceptance from the IHES-BIPS ethical committee. We have studied 100 patients with symptoms of pulsatile or non-pulsatile headache with or without photophobia, phonophobia, with duration of 30 minutes to 4 hours. Some have both symptoms while some remain asymptomatic. The pain in migraineurs is measured by using visual analogue scale.[27] The blood sample is collected from antecubital vein, then the CRP level along with serum magnesium level test in blood were performed by using slide method (by agglutination in presence of antibodies[28]) and biochemical analysing method (bio majestic analyzer) then the results are noted and taken under consideration. The treatment given to the migraineurs include divalproex, flunarizine and propranolol in separate or combination with one or two drugs.

After the initial visit, the migraines' are being told for the next visit after 1 month. But after 1 month, only 20 patients came for the review and for them, as mentioned above, serum magnesium level and CRP level were evaluated and before that pain scale was also measured. Treatment based on the results were given to migraineurs. Both parametric and non-parametric data have been noted. Variable data of pain scale and Magnesium level were compared pre and post treatment by Wilcoxon test and T-test. Non-parametric data of CRP were compared pre and post treatment by Mc Nemar test.

3. Results

20 patients, including 6 male and 14 females, have been evaluated. Average age in males and females were 15-38 years. The migraineurs containing the symptoms of pulsatile headache were 7 and non-pulsatile headache were 13. Sensory stimuli which triggers the headache in migraine patients were 3 with photophobia, 6 with phonophobia, patients with both photophobia and phonophobia were 10 and migraineurs with no sensory stimuli was 1. Classifications based on ICHD were done here and migraineurs were classified as: migraine without aura were 3, migraine with visual aura was 1 and with transformed migraine were 16. The treatment given to migraineurs was combined with other drugs or individual drugs. Treatment by Divalproex in 1; divalproex, flunarizine in 12; flunarizine, propranolol in 2 and divalproex, propranolol, flunarizine in 5 patients. The dosage of drugs was constant with Divalproex (250 mg), Flunarizine (10 mg), Propranolol (40 mg).

At the first visit, where the pain scale was significant with the mean difference of 3.90 and P=<0.001 significant. The C-reactive protein non-parametric data were taken under consideration. The negative–negative 2; negative–positive 3 and positive–negative 2; positive–positive 13 (first visit- second visit) (P=1.0) non-significant. The serum magnesium level was significant with the mean difference of -0.15 (P= 0.01).

The most common type in our study was transformed migraine. In some migraineurs treatment with Divalproex and flunarizine in combination was effective and in some,

the combination of Divalproex, Flunarizine and Propranolol remains effective.

We can see the changes in both pain scale and serum magnesium level. We can conclude that it is caused by the treatment given in patients because the effect of every drug leads to a decrease in migraine attacks. The combinations of two and three drugs gave a significant effect. But it's not significant to CRP. The major cause is not yet specified and further studies should be done to know its efficacy in a detailed manner.

Table 1: Demographic details of migraine patients

	No of patients	% of patients
Sex		
Male	6	30.00
Female	14	70.00
Age groups		
<=20yrs	3	15.00
21-30yrs	11	55.00
31-40yrs	6	30.00
Mean age	28.10	
SD age	7.11	
Headache		
Non pulsating	14	70.00
Pulsating	6	30.00
Duration		
30-60 min	4	20.00
60-120 min	2	10.00
120-180 min	5	25.00
180-240 min	1	5.00
240 min	8	40.00
Sensory stimuli		
Nil	1	5.00
Phonophobia	6	30.00
Photophobia	3	15.00
Photophobia and Phonophobia	10	50.00
Total	0	100.00

Table 2: Representing diagnosis of the patients

Diagnosis	No of patients	% of patients
Migraine without aura	3	15.00
Migraine with visual aura	1	5.00
Transformed migraine	16	80.00
Total	20	100.00

Table 3: Treatment given to the patients

Types of treatment	No of patients	% of patients
Divalproex (250mg)	1	5.00
Divalproex (250mg), Flunarizine (10mg) Propranolol (40mg),	5	25.00
Divalproex (250mg), Flunarizine (10mg)	12	60.00
Flunarizine (10mg), Propranolol (40mg)	2	10.00
Total	20	100.00

4. Discussion

A cohort, prospective and observational study performed and the outcome of pain scale, CRP and Serum Magnesium Level in migraine with the prophylactic treatment was noted. In this study, we use a visual analogue pain scale, which is a pure measurement of pain intensity from acute to chronic pain that is represented as 'no pain' or 'worst pain'.[29]

It is highly sensitive and applied to the wide variety of population and also easy to administer and analyse. C-reactive protein, the inflammatory marker, which is measured by different methods and assessment, is simplified. CRP is associated with other systemic vascular disease and chronic disease. It increases the serum CRP level in a patient with migraine before the treatment involves inflammatory processes in development or making migraine headaches.[30] Many studies were done to know the low serum magnesium level in migraineurs and treatment with magnesium supplements to see whether the intake of magnesium supplements can decrease the migraine attacks in migraineurs.

In previous studies, 11-point pain scale or visual analogue scale was 55% responsive may rummage out levels of differences between existing migraine medications.[27] In this study, the pain scale measures show the effect before and after the medication.

A study by Vanmolkot et al,[13] Welch et al[14] and Kurth et al,[15] which showed the increased CRP level in migraine without aura than compared with migraine with aura. But Vanmolkot et al[13] and Welch et al[14] did the study on a small group of patients than compared to the study by Kurth et al,[15] who had done it on 27,626 women, the results were also same as the above study, with an increase of CRP level in migraine without aura then migraine with aura. The study by Rockett et al[31] in obese and normal weight female in migraineurs and the CRP level was in normal range in migraine with aura and migraine without aura. But in contrast to those studies, the CRP level in patients of migraine with aura and migraine without aura and transformed migraine links with symptomatic pain in migraineurs. Study where there was high CRP level in migraineurs but no significant difference of CRP with different types of migraine[32] including migraine with aura and without aura.[33]

The study by Silva et al[34] showed there is no difference between the CRP values between cases and controls and Fava et al[35] study showed no significant difference of CRP values between groups. The Reykjavik study shows that CRP level increased among migraine sufferers compared

Table 4: Comparison between pre and post treatment of pain scale

Time	Mean	SD	Mean Difference	SD Difference	% of change	Z-value	P-value
Pre-test	6.20	1.54					
Post-test	2.30	1.42	3.90	1.86	62.90	9.3722	<0.001*

*unless indicated otherwise, difference between groups were not statistically significant($p<0.05$)

Table 5: Comparison between pre and post treatment C-reactive protein

Pre-test C-reactive protein	Post-test C-reactive protein			
	Negative	Positive	Total	%
Negative	2	3	5	25.0
Positive	2	13	15	75.0
Total	4	16	20	100.0
%	20.00	80.00	100.00	-

Table 6: Comparison between pre and post treatment Serum Magnesium level

Time	Mean	SD	Mean Difference	SD Difference	% of change	Paired t-test	P-value
Pre-test	1.76	0.21					
Post-test	1.90	0.25	-0.15	0.25	-8.26	-2.6137	0.0171*

to non-migraineurs. Migraineurs without aura had lower CRP values compared to non-migraineurs and migraine with aura, also in some young women migraineurs without aura who had a borderline higher CRP levels compared to migraineurs with aura and non-migraineurs.[36] In contrast to our study, the CRP level was increased or decreased in migraineurs at the first visit. But, on the second visit, the CRP levels either decreased or increased or remained constant as the first visit of the migraineur with the undergoing treatment.

There are several factors in the creator of migraine headaches, including several factors which include emotional factor, environmental factor and biochemical markers. The study by Masoud A et al,[37] Mauskop A et al[20] and Mukherjee et al[19] showed the relationship between serum magnesium level and migraine prophylaxis. Masoud A et al[36] showed that low Serum Magnesium level is found in the patient with migraine attack.

The study by Trauninger et al[22] showed decreased magnesium levels in migraine patients. Mauskop A et al[20] and Boska et al,[21] they both showed low levels of magnesium in migraine patients. A study in the National Institute of Neurology, Italy, Bussone[38] showed low levels of Serum Magnesium are being reported in migraine patients. Mean Serum Magnesium level during migraine attack was low and in pain-free time, it was slightly increased. There was a significant difference between Serum Magnesium during attack and pain-free period within the normal range.[32] It shows that decrease in Magnesium level in brain neurons causes decreased physiologic threshold for migraine attack.

Another study by Boska[21] has shown that low Magnesium level causes excitability of neurons and neuromuscular junctions. It may also result in hyperventilation, which can aggravate the effects of hypercarbia. Magnesium may regulate neuronal excitability and affect migraine headaches.[25] A study by Taylor FR showed the positive role of Magnesium in preventing migraine attacks.[39] A study by Koseoglu et al,[40] oral Magnesium Citrate supplementation significantly reduced the frequency of migraine attack in comparison with placebo. Under our study, initially the serum magnesium level was decreased in migraineurs but after the treatment, it has increased. So, we can say that prophylactic treatment given to migraineurs was effective.

Divalproex sodium, an anticonvulsant drug, shows that the greater clinical relevance was more than twice as likely to have 50% or large reduction in the number of migraine attacks.[41] Hering and Kuritzky[42] reported divalproex shows a tendency to lower the severity and shorten the episode of migraine more than placebo. In our study, the CRP level didn't vary from first visit to second visit but the pain has reduced and serum magnesium level has also decreased from the first instant. So, we can say that the single drug of divalproex cannot be effective.

The study shows that Flunarizine reduced headache frequency.[43] Flunarizine prophylaxis of migraine revealed an excellent effect in migraineurs.[44] Propranolol blocks platelet serotonin uptake in vitro and in vivo. There's a possibility that the effect of propranolol in migraine may be because of its effect on serotonin and is being tried in migraine.[22,23,35] The propranolol counteracts. In contrast to our study, single treatment with divalproex didn't show any major effect in the migraineurs. The combination of divalproex with flunarizine showed 15% of effect in the migraineurs while flunarizine combined

with propranolol showed 10% effect. With aspects to that, combining Divalproex, Flunarizine and Propranolol showed over 25% efficacy.

We can say that the most effective drug is the combination of three drugs which is Divalproex sodium, Flunarizine and Propranolol reduces the frequency of headache and this treatment should be continued for about 6 months then stopped under the guidance of the physician.

5. Conclusion

This study concludes that the C-reactive protein and Serum Magnesium level in pre and post-treatment varies but CRP level in many migraineurs remains unaffected. Pain in these patients decreases, Serum Magnesium level gets affected and the number of episodes in migraineurs also get affected, in some there are 4-6 while in some there are none to 1. There was a decrease in the review of patients after the first visit. As in previous trials, which show the effect of low serum magnesium level effect in triggering migraine attack and increased CRP level in effect of migraine.

Prophylactic treatment in previous studies was done differently or vaguely compared with placebo. In our study, we defined the effect of drugs on the Serum Magnesium level and CRP level to decrease the frequency of attack and to decrease migraine headaches. We would like to recommend further study like this with more patients to get more distinctive outcomes. Finally, it has been concluded that with the help of prophylactic treatment, CRP level gets increased and Serum Magnesium level gets decreased and there are mild changes in the symptomatic migraineurs too.

6. Conflict of Interest

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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