An open label comparative prospective study of proprietary formula migradep®) versus propranolol for chronic prophylaxis migraine

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Abstract
Due to the involvement of different pathophysiologic factors in aetiology of migraine including but not limited to neuro-inflammation, involvement of CGRP(Calcitonin Gene Related Peptide) and the two newly discovered pathomechanisms; the metabolic energy deficit and the overload of oxidative stress as a trigger for migraine attack and a contributing factor to increased severity of the attack. The current dilemma is that the current medications used in the practice do not address those pathomechanisms. All these challenges have led to the need for a solution with more comprehensive mechanisms of action or a multiple target formula to be used as an alternative solution to tackle the different factors involved in Migraine Pathophysiology and at the same time to improve the response and QoL to migraineurs. In addition to the challenges of multiple pathophysiologic factors another factor necessitates the search for an alternative medications that do not have the contraindications of neither the acute medications nor the available oral chronic prophylactic medications. This study was an open label prospective, which highlights the comparisons between the efficacy of the fixed dose combination migradep (Parthenolide 6.25 mg, Riboflavin 25 mg, Coenzyme Q10 100mg, Magnesium Oxide 200mg, Ginkgolide B 60 mg, microencapsulated Lactobacillus acidophilus 2 Bln CFU and microencapsulated Bifidobacterium Lactis 2 Bln CFU) (sixty three patients) versus propranolol 80 mg(forty nine patients) in the prophylaxis of chronic migraine diagnosed in congruence with the set criteria by the international headache society. Responding rate and efficacy, intensity of attack and severity, duration of attack, compliance and tolerance to the treatment on monthly basis for three consecutive months, is what patients were evaluated on. migradep has more significant efficacy than propranolol. No significant side effects reported for both treatment groups. Our results show that oral migradep intended for migraine prophylaxis is efficacious and well-tolerated prophylactic option for chronic migraineurs. It has better efficacy than propranolol and has comparable tolerance profile. Migradep may be an alternative strategy for migraine prophylaxis, however, larger comparable trials are needed to confirm these results.
KeyWords: Migraine Prophylaxis, Propranolol, Parthenolide, Magnesium, CoQ10, migradep®

1. Introduction

Migraineurs share devastating sufferings; around 15% of patients with chronic migraine suffer from more than two attacks monthly (1). The implications that are brought about by chronic migraine, which is reflected upon patients as well as society in large scale is of high importance since its high prevalence comes at the peak age of productivity. (2, 3) The need for prophylaxis therapy by migraineurs is estimated to be around 38%. Of note, 3-13% of migraine sufferers use chronic prophylaxis. (4,5) Intolerance to chronic preventive therapy among migraineurs showed the highest rate toward the following adverse effects, weight gain, memory loss, depression and somnolence. (6,7,8,9) The most common prophylactic medications used in for migraine are; amitriptyline, beta blockers, flunarizine, and tricyclic antidepressants. (10,11). Furthermore, there is considerable rate of patient dissatisfaction due to failure to achieve optimal control (12) AAN, EFNS together Canadian Headache Society gave strong rating to Riboflavin, Magnesium, feverfew (Parthenolide) to have level B recommendation. (13,14) Based on findings of an RCT published by AAN coenzyme Q 10 showed superior efficacy to placebo with augmenting efficacy to riboflavin being both are metabolic enhancers. Conclusion from this RCT stated coenzyme Q10 to be efficacious and well-tolerated. (15) Dysbiosis has been implicated to contribute to trigger migraine through its communication by gut-brain-axis. The leaking of CGRP and Cytokine L10 and Serotonin; this has led to the idea that probiotic has a role in migraine prevention.(16) The role of probiotic in reducing chronic migraine suffering has been proved by randomized controlled trial.(17) Another trigger factor to migraine is oxidative stress which has been shown to produce high energy production by the mitochondria, altered membrane properties of the mitochondria, calcium overload and excitotoxicity, neuroinflammation and activation of microglia.(18) This pathogenetic mechanisms will be encountered by multiple antioxidant molecules in the used formula in the research. In spite of the variety of

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literatures and researches that discussed the efficacy of the combined effects of parthenolide, magnesium, coenzyme Q 10 and riboflavin, there is no study compared this unique fixed dose combination with beta blockers. Of note, propranolol is one of the main choices in first line in migraine preventive therapy. Further to that, the combination addresses newly discovered pathogenetic factors in migraine, like gut-brain-axis and oxidative stress and homocysteine neurotoxicity. In this study, we compared the efficacy of a unique combination of bioactive ingredients to that of beta blockers.

2. Methodology and Materials

This is a prospective open label comparative pattern study for two protocols to be used in migraine Prophylaxis. (112) patients (female =100, Male:12) were assigned to receive either migradep capsule at a dose of once daily or Propranolol in the usual eighty mg. The duration of treatment was 12 weeks intervention that comprises of follow-up every four weeks. The patients were distressed and experience low quality of life due to the chronic migraine with aura and without aura.

Criteria set by the ICHD-II, directed the diagnosis that was made. Guidelines from the Declaration of Helsinki and the Strengthening the Reporting of Observational studies in Epidemiology (STROBE), was what was utilised to conduct the study

The study was approved by Research Ethics Committee at Hawler Medical University/ College of Medicine and assigned to the principal investigator. Every patient was well-informed of, verbally consented and undertook the full neurological, in addition to, the physical assessment. Parameters relating to haematology and biochemistry were checked, before entering.

Patient Selection

Our criteria of inclusion were: A subject would be considered eligible for inclusion in this study, only if all the below criteria were fulfilled at base line

Eligibility for the subject to partake in the trial was conditional upon the fulfilment of the following criteria during the base line: (1) Diagnosed as migraine with aura MO or migraine without aura MA which is according to the criteria used to diagnose, and is stated by ICHD-II, (2) Age of the patient at first onset ≤ 50 years old. (3) Between two to six migraine attacks per month, including the average migraine attack of two and six times per month, during the baseline period. Age of participants in this research range was between eighteen 18 and sixty-five 65 years old. Our exclusion criteria were: If a single or multiple points from the criteria are applicable, then the subject will automatically be ineligible to partake in the trial.

(1) Usage of analgesics more than ten times per month for acute headache relief (2) Three months prior to the inclusion, a prophylactic medication has been consumed to prevent a migraine, such as beta blockers, calcium channel blockers, anti-epileptic drugs, antidepressants and 5-HT receptor blockers. (3) Any drug abuser was taken or alcohol was consumed (4) comorbid primary diseases including cardiovascular, cerebrovascular, liver, kidney, hematopoietic system disease, etc. (5) patients suffering from psychiatric illness(6) Presented an allergic reaction to the trial drugs. (7) Pregnancy and lactation. (8) Patients on Warfarin.

3. Assessment

Responder rate (defined as the percentage of patients in the treatment group whom achieved fifty % or greater reduction in attack frequency during treatment compared with the baseline period, was the primary outcome measure.

Intensity of migraine attack frequency paired along with the duration of attack and patient reported outcome based on Migraine diary, was the secondary outcome measure. Adverse effects have been monitored during the trial period.

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Patients whom were congruent to our criteria were evaluated every month and they were having open access call during the treatment period. They were advised not to take analgesia unless if necessary needed. They have been also advised and given a printed diary to record their complaints and the progress of the treatment.

During the initial visit (V1), along with the agreed upon verbal consent, the physician will collate the demographic data of each patient. This will be in addition to other sets of data such as migraine clinical phenotype characteristics, past medical history, previous migraine history, used medications, information on migraine attacks and associated symptom. After V1 there was monthly assessment at V2 (V2; Day30 ± 14 Days since V1). Up until the completion of the V3 study (Day 120 ± 10), the patients had all kept a diary of migraine to report the changes they have been told about as mentioned here in the study.

At the completion of the first month, all enrolled subjects undertook a reassessment attested by the responding rate of 50%, duration of attacks, the severity. Those whom withdraw from the treatment or they were intolerant, their status has been excluded and recorded.

Evaluation of Efficacy

The targeted aim of this study wants to investigate whether migradep represents an alternative option for chronic migraine prophylaxis.

The patients enrolled into the study were divided into two groups. The patients whom received migradep were 63. The patients whom received propranolol were 51. The demography in term of gender for the whole studied sample was 13.3% of patients were male versus 86.7% were female. The

first group received one capsule of migradep with mid-day meal and the patients were reassessed after one month. The second group patients received propranolol 80 mg divided as 40 mg twice daily. All patients were followed monthly for 3 months where attack frequency, intensity, duration and the number of needed rescue pills and drug side effects were noted. The evaluation was done by the consultant neurologist; the principal investigator himself; on monthly basis, based on the filled migraine diary by the patient and the face-to-face assessment at the clinic. Parameters Check in the Results based on recognized questionnaire were: Responder Rate, No. Migraine Attacks, VAS (Visual Analogous Score), Total Duration of Migraine Attacks and Tolerability.

Safety Evaluation

The available and cumulative evidence illustrate that supplementing patients with these specific active ingredients is well-tolerated in the majority of patients (Holland S, Silberstein SD, Freitag F et al, 2012). In this context there were no anticipation for any serious adverse effects to take place in this study. Nevertheless, all patients were motivated to report their adverse effects and to share with the physician. Tight follow up towards this issue has been in place.

Statistical Evaluation

The data of the study were stored in Microsoft excel spread sheet and analyzed on the computer using the SPSS software 20 and Microsoft excel program (2010). Numeric variables were expressed as mean ± SD and all statistical comparisons were made by means of independent t-test with P ≤0.05 was considered statistically significant. Categorical variables were expressed as numbers and analyzed by cross tabulation to assess the frequency and percentage of each variable among studied groups. The correlation was done between all parameters using Chi square to test the relationships between categorical variables with P ≤0.05 was considered statistically significant.

4. Results

The results illustrated in table (1) revealed that there were non-significant difference in the age between the two studied group whereas significant differences were obtained between patients receiving migradep and those receiving Propranolol in that migradep showed a significantly (p=0.01) higher response than Propranolol (63.58±21.68 and 52.96±20.59; respectively) with a significantly lower intensity that ranged from mild to moderate intensity in comparison with patients receiving Propranolol who showed mainly moderate intensity of attack in post-treatment period. Furthermore, patients receiving migradep showed a significant reduction in the duration of migraine attack after 12 weeks of treatment.

Table (1): The comparison of the studied parameters between patients receiving migradep and Propranolol by independent t-test

P value	Propranolol N=49 mean±SD	Migradep N=63 mean±SD	Parameter
0.154	32.59±9.34	35.22±9.83	Age
0.01	52.96±20.59	63.58±21.68	Response
0.002	2 ± 0.87	1.51± 0.74	Intensity of Attack Post-treatment
0.011	18.14± 16.3	11.52±10.77	Duration of Migraine/ 12 Weeks Post Treatment (hours)

Results demonstrated in table (2) showed that there were highly significant (p<0.001) decrement in the intensity of attack and the duration of migraine after receiving either migradep or Propranolol. The results showed that the reduction in the intensity of attack and the duration of migraine was more pronounced in the patients whom were using migradep. The intensity in migradep group reduced from a severe state to a mild to moderate intensity after 12 weeks of treatment and at the same time the duration of the attack reduced to about one fourth that before receiving it.

Table (2): Comparison in the intensity of attack and the duration of migraine before and after receiving migradep and Propranolol

P value	Duration of Migraine mean±SD	P value	Intensity of Attack mean±SD	Parameter	
<0.001	40.62±26.99	<0.001	3 ± 0	Pre-treatment	Migradep (N=63)
	11.52±10.77		1.51± 0.74	post treatment	
<0.001	36.78±30.95	<0.001	3 ± 0	Pre-treatment	Propranolol (N=49)
	18.14± 16.3		2 ± 0.87	post treatment	

Data demonstrated above were confirmed by the results which clarify the effect of migradep and Propranolol administration on the intensity of the attack after treatment. Table (3) showed that the majority of patients received migradep experienced a mild to moderate attack after receiving the treatment whereas about one third of cases received Propranolol suffered from severe attacks. This is also supported by Chi square results that showed significant moderate association between the type of treatment used and the intensity of post-treatment attack as shown in table (4).

Table (3): Drug Cross tabulation after treatment with Migradep and Propranolol					
Intensity of Attack Post-treatment * Drug Crosstabulation					
			Drug		Total
			migradep	Propranolol	
Intensity of Attack Post-treatment	No Attack	Count	6	1	7
		% within Drug	9.5%	2.0%	6.2%
	Mild Attack	Count	22	15	37
		% within Drug	34.9%	30.6%	33.0%
	Moderate Attack	Count	32	16	48
		% within Drug	50.8%	32.7%	42.9%
	Severe Attack	Count	3	17	20
		% within Drug	4.8%	34.7%	17.9%
Total		Count	63	49	112
		% within Drug	100.0%	100.0%	100.0%

Table (4): Chi-Square Tests for association between the treatment used and the intensity of the attack)			
		Value	Approx. Sig.
Nominal by Nominal	Phi	0.407	0.000
	Cramer's V	0.407	0.000

Additionally, table (5) revealed that migradep administration reduced the number of cases that suffered from severe attacks to only about 4.8% of them before treatment with about 9.5 % of cases showed no-attack which also confirmed by chi square results which illustrated that there was a highly significant strong association between the intensity of attack pre- and post-treatment with the administration of migradep as listed in table (6).

Table (5): Intensity of Attack Pre-treatment and post treatment with migradep					
Crosstab					
			Treatment		Total
			Pre-treatment	post treatment	
Intensity of Attack	No Attack	Count	0	6	6
		% within Treatment	0.0%	9.5%	4.8%
	Mild Attack	Count	0	22	22
		% within Treatment	0.0%	34.9%	17.5%
	Moderate Attack	Count	0	32	32
		% within Treatment	0.0%	50.8%	25.4%
	Severe Attack	Count	63	3	66
		% within Treatment	100.0%	4.8%	52.4%
Total		Count	63	63	126
		% within Treatment	100.0%	100.0%	100.0%

Table (6): Chi-Square Tests for association between the attack pre and post treatment with migradep			
		Value	Approx. Sig.
Nominal by Nominal	Phi	0.953	0.000
	Cramer's V	0.953	0.000

Furthermore, Propranolol showed results close to that of migradep but with less pronounced effect on the severe cases that reduced to about one third of their original as shown in table (7) and confirmed by the chi-square results illustrated in table (8) which revealed a strong significant association between the administration of Propranolol and the intensity of attack before and after receiving the treatment.

Table (7): Intensity of Attack Pre-treatment and Post treatment with Propranolol					
			Treatment		Total
			Pre-treatment	post treatment	
Intensity of Attack	No Attack	Count	0	1	1
		% within Treatment	0.0%	2.0%	1.0%
	Mild Attack	Count	0	15	15
		% within Treatment	0.0%	30.6%	15.3%
	Moderate Attack	Count	0	16	16
		% within Treatment	0.0%	32.7%	16.3%
	Severe Attack	Count	49	17	66
		% within Treatment	100.0%	34.7%	67.3%
Total		Count	49	49	98
		% within Treatment	100.0%	100.0%	100.0%

Table (8): Chi-Square Tests for association between attacks pre and post treatment with migradep			
		Value	Approx. Sig.
Nominal by Nominal	Phi	0.696	0.000
	Cramer's V	0.696	0.000

Patients reported side effects

Both groups showed comparable adherence to treatment. In regard to migradep arm there was mild gastric upset in two cases, while two patients in the arm of propranolol suffered from fatigue and depression. Two patients from the enrolled group did not continue treatment on propranolol for unknow reason. (They were not responding to call and they did not return for further follow up).

5. Discussion

The physiopathology of migraine goes beyond the major disturbed functioning of the sub-cortical structures modulating sensory input in the trigemino-vascular system. Thus, CGRP, nitric oxide and the pain mediator substance P are released from trigemino-vascular neurons, thus leading to intensifying vasodilation and producing neuroinflammation. (19,20). Of note to mention NO is considered as a key molecule in migraine pathophysiology. Of note to mention some critical factors; among others; that produce migraine like, mitochondrial dysfunction, increment in calcitonin in addition to decrement in the level of metabolic enzymes. Mitochondrial dysfunction leads to increment in neuronal excitability, this is eventually considered as a migraine trigger factor and render the patient more prone to migraine (21,22,23,24). Neuroinflammation and its correlation to the spreading of cortical depressions is well-established and considered as a factor contributing to migraine pathogenesis (25,26) New researches and findings are pointing to the involvement of redox status imbalance as a triggering factor to migraine (27)

In this context, we can see that Chronic migraineurs (CM); of which large proportion; still face unmet needs. The suboptimal use, the adverse effects, the contraindications, the limited efficacy and the low rate of adherence to oral preventive therapies for migraine. (28,29,30). This has changed the strategies of treatment options that achieves the following targets: 1) fewer side effects, 2) more addressing the unmet needs in pathophysiologic factors involved in migraine and 3) has more patient preference. Among those are: onabotulinum toxin–A, monoclonal antibodies and external neurostimulators. (31,32) and there is a fast-growing trend toward the use of CAM among them nutraceuticals (33).

There is a trend among the migraineurs whom are chronically suffering to search for safer, more tolerable and lesser side effects. Drugs like propranolol sometimes like other first line preventive medications might carry a risk of very severe side effects like depression, erectile dysfunction, bradycardia and hypotension, especially when used in high doses. (Migraine headache prophylaxis, AAFP, Jan, 1, 2019)

This option has found its way due to the availability of evidence-based guidelines backing up the use of those nutraceuticals of the class B that supports the use of nutraceuticals like, riboflavin(vitamin B2), magnesium, coenzyme Q 10, and parthenolide(feverfew). An approved antidepressant medicine from the class of TCA was approved at a rating status of an evidence with low to moderate. (34, 35, 36). This conforms with the status in the evidence for the active ingredients in migradep. The German guidelines for headache also confirm the aforementioned status and power of evidence for supplements used in preventative treatment of chronic migraine(37). The guidelines of headache in Canada CHS have given a strong recommendation in migraine prophylaxis for vitamin B2, CoQ10 and magnesium. Feverfew has gained strong recommendation with moderate quality of evidence. Those nutraceuticals have found its place among topiramate, propranolol, amitriptyline and flunarizine. The acknowledgement of the authors of the CHS guidelines comes based on the cumulative study findings and due to the well-established safety and tolerability among users (38).

In the current fixed dose combination, the anticipated benefit might be gained from the added-value ingredients that stems from the mechanisms of action that this FDC used in this study apply on gut brain axis and oxidative stress; having 5 antioxidants and special strains of probiotic. Dysbiosis of GI microbiota and leads to increment gut-leaky-phenomenon which eventually lead to induction of HPA axis through the release of proinflammatory cytokines, like, IL-1β and TN. which eventually results in inflammatory burden. CGRP signalling also could be affected by microbiota, hence a bidirectional relationship. (39, 40, 41). Thus, the amendments of this dysregulated microbiota in GIT will have a probable value helping to assist in some migraine associated features (42).

Mitochondrial dysfunction is documented in previous clinical studies to contribute in migraine physiopathology (43,44). In studies using Magnetic resonance spectroscopy, it has shown decreased interictal rates of mitochondrial oxidative phosphorylation in the brains of migraineurs[43, 44, 45]. Riboflavin; according to recent updates, have proved neuroprotectant potential via amelioration of redox stress, neuro-inflammation, and glutamine excitotoxicity via diverse mechanisms of which homocysteine neurotoxicity is very plausible mechanism and its antagonists are considered among the preventative treatment option for

migraine (46, 47).

Depletion of Mitochondrial energy is highly investigated as a one of the main aetiologies of migraine [44, 45, 48]; for this reason, supplementing migraineurs with coenzyme Q10 could be a preventive for migraineurs via replenishing the store and at the same time as a metabolic enhancer. Taking CoQ10 leads to decrement in CGRP, which is considered one of the main inducers of migraine pathophysiology (49) Increment in the susceptibility to migraine has been thoroughly studied to be associated with magnesium deficiency.(50,51,52)

Feverfew, or its active extract parthenolide, is a phytotherapy used in medicine for centuries and for a wide range of diseases. Parthenolide has been examined how to be a valuable agent affecting the processes that are involved in aetiology and induction of migraine [53] and display antimigraine actions, for instance the prevention of nitric oxide synthesis and cytokine production and inhibition of CGRP induction, as well. It also affects promotion of serotonin release from platelets [54].

A randomised controlled trial evaluating the usage of fixed dose combination of the following nutraceuticals (feverfew, coenzyme Q10, riboflavin, and magnesium) established favorable outcomes [55] Ginkgolide B(GB), phytochemical extract from the herb leaves of Ginkgo biloba acts to modulate the action of glutamate in CNS (56) GB has revealed to be effective in reducing MA frequency and duration. This effect can be seen in the first two months of taking the phytochemical extract of GB and this effect is further improved during the period of 60-120 days from the beginning of the treatment. (57) Of note to mention, there is a current trend to focus gut-brain-axis as an important factor in development of migraine attacks (58,59). This triggering factor to migraine attacks has been dealt with the specific probiotic strain in migradep the fixed dose combination which might be one of the explanatory factors for the shown efficacy of migradep.

In the current work, we observed clinically and documented in a statistical basis the improvement gained by migraineurs as checked by the primary and the secondary outcomes measured after three months of supplementing the fixed dose combination of (parthenolide, magnesium oxide, riboflavin, ginkgolide B and the specific Lactobacillus and Bifidobacterium specific strains).

The demographics of age were between 30–40-year-old and the prevalence was higher in female 89.2% versus 10.8% in male which conforms approximately with other findings as it is reported by (dandan chen, et al, 2019). The response rate that reflects efficacy based on the reduction in frequency of attack showed significantly high response rate in favour of migradep (63.58%) compared to (52.96%) in patients whom were receiving propranolol, at a p=0.01. In reference to the intensity and the duration of attack both propranolol and migradep achieved significant reduction after initiating treatment, though the reduction was more pronounced with migradep than it was with propranolol as per the reduction in intensity. This has been shown in the majority of patients who received migradep they experienced a mild to moderate attack after receiving migradep while one third of patients in the arm of propranolol suffered from severe attack post treatment. This result is confirmed by Chi square as shown in Table 4. Furthermore, a highly significant association has been shown with the usage of migradep which achieved no attack after treatment at a percentage of 9.5% from the total number of patients whom had received migradep, whereas, it was only 2% in the group of patients whom had received propranolol. In reference to the duration of attack, patients receiving migradep exhibited a pronounced significant reduction in the duration of migraine attack when compared to patients receiving propranolol after 12 weeks of treatment, as shown in table 2.

The patients' trust was evident throughout the study period. They willingly continued their re-filling of migradep. Satisfaction of patient and decision to continue any specific preventive treatment for three months reflects that the patient whom were using migradep have experienced considerable improvement in their daily life, besides, no significant issue of intolerance has been in place to make patients non-adherent to the preventive treatment. In this migradep has shown promising results as an effective and tolerable preventive supplement for chronic migraineurs.

Limitation of this study

Absence of blinding, controlled group and randomisation might represent a limitation to this study. Nevertheless, there was no association between the distribution of gender and the agent used in both arms, which might decrease the biased assessment.

However, it was rather difficult to do this design as it is in other similar studies.

Yet, these factors have to be acknowledged as a limitation.

6. Conclusion

This study shows the migradep as a fixed dose combination has higher efficacy than propranolol and represents an equally tolerable alternative preventive option for chronic migraineurs. It can be be a new option to the armamentarium of migraine prophylaxis in patients whom have contraindications or intolerant to established preventive therapies. As this study represents the first of its type for this proprietary formula, we recommend larger sample study and a randomized controlled design is warranted. Since chronic migraine sometimes might need multiple medications, hence, its use can be another option

to be added to the armamentarium of migraine prophylaxis to optimise response. Migraine prophylaxis medications still a rich area for more exploration and investigations.

7. Funding

No funding was obtained for this study.

Availability of data and materials

Datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing Interest:

The principal investigator discloses no financial relationship of any kind of interest.

Abbreviations

CGRP: Calcitonin Gene Related Peptide
QoL: Quality of Life
CFU: Colony Forming Unit
AAN: American Academy of Neurology
EFNS: European Federation of Neurological Society
ICHD-II: The International Classification of Headache Disorders-II
5-HT: 5-Hydroxytryptamine
NO: Nitric Oxide
CAM: Complementary Alternative Medicine
AAFP: American Association of Family Physicians
CHS: Canadian Headache Society

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