

Clinical efficacy of melatonin for prevention of common migraine headache in comparison with propranolol

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Abstract

Migraine is a common primary headache disorder with a wide spread mechanisms that explain it's pathologyphysiological and there is no exact single theory that can determine the etiology of this disorder .The successful abortive treatment is obscure tell now a day, indicating prophylactic measures to decrease frequency , severity and duration of headache attacks. Propranolol is one of FDA approved drugs for the common migraine prevention where its chronic therapy reduces the frequency and severity of migraine in 60 to 80 percent of patients . Melatonin a pineal gland hormone that has ability for circadian rhythm control and was linked to migraine several ways. Both episodic (55%) and chronic (62.5%) migraineours reported waking up in the morning with headaches or being woken up at night by the headache . In addition, headaches occurring in the morning period have been attributed to sleep disorders. The present study was carried out to determine the efficacy of melatonin 5 mg daily for prevention of common migraine in comparison with propranolol 40 mg twice daily for 41 patient having for full criteria of common migraine headache with assessment of AST , ALT, Scr for all patients to ensure the safety of investigated drugs .The study concluded that melatonin has no significant difference than that of propranolol efficacy in the common migraine prevention and approved safety .

الفعالية السريرية للميلاتونين للحماية من صداع الشقيقة الساند بالمقارنة مع البروبرانولول

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كلمات المفتاح :- الميلاتونين ' صداع الشقيقة' الحماية.

الخلاصة

يعد داء الشقيقة من الاضطرابات الرئيسية الشائعة لآلام الرأس ، وهناك الكثير من الآليات التي فسرت ذلك الاضطراب الفسلجي المرضي ولكن لاتوجد هناك نظرية مفردة بإمكانها أن تحدد المصدر الرئيس المسبب لهذا الاضطراب. و مازال الى يومنا هذا العلاج المجهض للألم مفقودا ليعطي إشارة الى أهمية أساليب العلاج الأتقائي لتقليل مرات حدوث النوبة وشدتها وطول فترة حدوثها. البروبرانولول احد الأدوية المعتمدة من قبل منظمة الغذاء والدواء العالمية لعلاج داء الشقيقة الساند حيث أن الاستخدام المزمن لهذا الدواء يقلل من تكرار وشدة داء الشقيقة بنسبة 60-80% من المرضى.

الميلاتونين هو الهرمون المفرز من الغدة الصنوبرية وله القابلية للسيطرة على النظام اليوماوي وارتبط بداء الشقيقة بطرق عدة. مرضى داء الشقيقة بنوعيهما النوبي بنسبة 55% والمزمن بنسبة 62% يستيقظون صباحا مع صداع بالرأس أو يستيقظون ليلا بسبب الصداع بالإضافة الى أن الصداع الذي يحدث في فترة الصباح سببه الاضطرابات الحاصلة أثناء النوم.

نفذت الدراسة الحالية لتحديد فعالية الميلاتونين 5 ملغم يوميا لعلاج داء الشقيقة السائد مقارنة باستخدام البروبرانولول 40 ملغم مرتين باليوم حيث اخضع 41 مريضاً للعلاج كونهم مصابين بالصفات الكاملة لمرض الشقيقة السائد حيث قيمت مستويات انزيمات الاسبارتيت ترانسامينز والالنين ترانسامينز وكذلك الكرياتين المصل لجميع المرضى للتأكد من سلامة الأدوية الموصوفة. استنتج من الدراسة بان الميلاتونين ليس لديه فرق معنوي مع كفاءة البروبرانولول في علاج مرض داء الشقيقة السائد وكذلك في سلامة الأدوية .

INTRODUCTION

Migraine is a common disabling primary headache disorder of high prevalence and high socio-economic and personal impacts. It was classified into three major types; migraine with aura (classical migraine) ,migraine without aura (common migraine) and migraine variant⁽¹⁾ .

There were several studies for explanation of common migraine pathophysiology (vascular ,neurological or combination of both) but there is no exact mechanism can fully explain migraine pathogenesis^(2,3,4) .

There was no specific treatment algorithm for the management of common migraine and the headache attacks still occur after treatment time profiles^(5,6) , prophylactic measures are been used to decrease the frequency ,severity and duration of attacks⁽⁷⁾ .

The mechanism of action of preventive treatment that has proven effective in migraine prophylaxis are varied, no single medication has emerged as a clear treatment of choice whereas preventive measures are specific cases of migraineurs⁽⁷⁾ .

Propranolol has been approved by FDA migraine prophylaxis where studies have found that chronic therapy with propranolol reduces the frequency and severity of migraine in 60 to 80 percent of patients^(8,9) .

Melatonin and migraine are linked in several ways. Clinical symptoms may fluctuate, some patients reporting their headaches predominantly or specifically at a certain period of the day. Both episodic (55%) and chronic (62.5%) migraineurs reported waking up in the morning with headaches or being woken up at night by the headache⁽¹⁰⁾ . In addition, headaches occurring in the morning period have been attributed to sleep disorders⁽¹¹⁾ .

The aim of this study to compare the effectiveness of melatonin for migraine prevention in comparison within FDA approved propranolol .

PATEINTS, MATERIALS AND METHODS

This study was conducted in Al-Hussain teaching hospital in kerbala city from December 2012 till February 2014.

Forty one common migraineurs patients were enrolled in this study, all of them were having no co-morbidity, they are divided into two groups. Group 1 include twenty one patient treated by melatonin 5mg tablet (Vitane Pharma, USA) daily, whereas group

2 include twenty patient treated by Propranolol 40 mg tablet (Astra zenica uk) twice daily .

All participant patients have been investigated the following tests before the starting treatment then after 1, 2 and three months of treatment .

- 1- Severity (5-point) score⁽¹²⁾.
- 2- Frequency of attacks per last week of last month.
- 3- Aspartate Aminotransferases (AST) deterrmtnation⁽¹³⁾.
- 4- Alanine Aminotransferases (ALT) determination⁽¹³⁾.
- 5- Serum creatinine determination (Sr.cr)⁽¹⁴⁾.

The first and second measures to asses efficacy of investigated drugs while the 3rd , 4th and 5th tests to assess the safety.

The statistical analysis was performed by GraphPad Prism (version 5.01) includes:

1. Mean \pm Standard error of mean(mean \pm SEM).
2. One way analysis of variance ANOVA was used to examine the difference of raw data parameters among the same groups withen time intervals. The results of analysis with P values <0.05 was considered significant difference
3. Two way analysis of variance ANOVA (was used to examine the difference of the mean of parameters test between the study groups).The results of analysis with P values <0.05 was considered significant difference .

RESULTES AND DISCUSSION

Table (1) showed the effect of treatment of the group1 (melatonin 5mg daily) and group 2 (propranolol 40 mg twice daily as control) on severity of attacks (5-points) score of common migraine patients after 1, 2 and 3 months.

It is obvious that there are changes in the severity score value regarding to type of studied drugs as compare to the control one and also regarding to investigated time intervals as compared to base line. Statistical analysis of individual data within groups applying ANOVA one -way analysis showed that there is statistically significant difference($p<0.05$) after 1,2 and 3 months of treatment when compared with the baseline values for the all groups.

The above findings were indicating the role of the studied treatment on decreasing of severity of attacks in patients with common migraine headache , within the investigated time intervals.

Statistical analysis of individual data between groups (i.e. group 1 versus group 2) applying ANOVA two-way analysis(table 1) showed that group 1 have no significant difference ($P\geq 0.05$) as compared to group 2 severity of attacks scores indicating that there is no efficacy difference in between melatonin and propranolol

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Melatonin has anti-inflammatory properties via down-regulation of proinflammatory cytokines⁽¹⁵⁾ and inhibition of nitric oxide and methylenedioxyamphetamine (MDA) production⁽¹⁶⁾. The neurogenic inflammation is responsible for the pain of migraine⁽¹⁷⁾ . This can explain the activity of melatonin in decreasing the severity of migraine attacks.

Table (2) showed the effect of treatment of group1 (melatonin 5mg daily) and group 2 (propranolol 40 mg twice daily as control) on frequency of attacks of common migraine patients after 1, 2 and 3 months. It is obvious that there are changes in frequency of attacks value regarding to investigated time intervals as compared to base line.

Statistical analysis of individual data within group applying ANOVA one -way analysis showed that there was statistically significant difference($p < 0.05$) after 1,2 and 3 months of treatment when compared with the baseline values for the all groups. The above findings were indicating the role of the studied treatment on decreasing of frequency of attacks within the investigated time intervals.

Statistical analysis of individual data within groups (i.e. group 1 versus group 2,) applied ANOVA two-way analysis(table 2) showed that group 1 patients frequency of attacks have no significant value ($P \geq 0.05$) as compared with group 2 after 1, 2 and 3 months of treatment .

Melatonin has a sedative effect⁽¹⁸⁾. Melatonin is thought to potentiate the effects of gamma-amino butyric acid (GABA) via direct interaction with GABA receptors^(19,20). Research indicates that melatonin exerts a sleep-promoting action by accelerating sleep initiation, improving sleep maintenance, and marginally altering sleep architecture⁽²¹⁾ and since high percent of the common migraineurs patient having sleep disturbance as trigger factor⁽²²⁾ , whereas the frequency and occurrence of migraine attacks in any individual depends strongly on their CNS response to migraine specific triggers⁽¹⁸⁾ , of which one of them is sleep disturbance⁽²²⁾ . This can explain the activity of melatonin in decreasing the frequency of migraine attacks.

Table (3) showed the effect of treatment of group1 (melatonin 5mg daily) and group2 (propranolol 40 mg twice daily as control) on the Serum Aspartate Aminotransferases (AST) level of common migraine patients after 1, 2 and 3 months. It is obvious that there are no significant changes ($P \geq 0.05$) in the enzyme levels regarding to investigated time intervals as compared to base line for both studied drug and control one.

Previous studies have shown that melatonin does not cause a significant increase in AST level^(23,24) and this agree with present study finding.

Table (4) showed the effect of treatment of group1 (melatonin 5mg daily) and group 2 (propranolol 40 mg twice daily as control) on the Serum Alanine Aminotransferases (ALT) level of common migraine patients after 1, 2 and 3 months. It is obvious that there are no significant changes($P \geq 0.05$) in the enzyme levels regarding to investigated time intervals as compared to base line for both studied drug and control one.

The study finding regarding to melatonin safety compatible with other studies that explain the safety of melatonin where as it has no effect on ALT enzyme level^(23,24).

Table (5) showed the effect of treatment of group1 (melatonin 5mg daily) and group 2 (propranolol 40 mg twice daily as control) on the Serum creatinine level of common migraine patients after 1, 2 and 3 months. It is obvious that there is no significant changes in the serum creatinine levels regarding to the type of studied drugs as compare to investigated time intervals as compared to base line for both studied drug and control one .

These finding demonstrate that the safety of melatonin was comparable to that of propranolol in the prevention of common migraine.

The study finding regarding the effect of melatonin on serum creatinine explained as melatonin cleared 90% via hepatic sulfate and to lesser extent by glucouronide conjugation (pharmacologically inactive compound)⁽²⁵⁾.

Conclusion and Recomendation

The result of this study reviled that melatonin has similar efficacy to the FDA approved drug propranolol in the common migraine prevention within comparable safety for AST, ALT and serum creatinine point of view, whereas melatonin might be recommended as an option of choice for common migraine prevention to the patients that are not well tolerated to propranolol.

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Table 1 : Effect of treatment with group 1 (Melatonin 5mg daily) and group 2 (Propranolol 40 mg twice daily as control) on severity of attacks (5-points) score ,after 1,2 and 3 months of treatments.

Group no.	Severity(5-point scale) score value			
	Before treatment	After 1 month	After 2 months	After 3 months
1 (n=21)	4.95±0.04	3.28±0.31 ab	3.33±0.37 ab	3.23±0.40 ab
2 (n=20)	4.8±0.04	3.2±0.17 a	3.05±0.19 a	3.1±0.19 a

values are presented as mean ± stander error of the mean SEM.

a significantly difference (P<0.05) as compared with baseline (before treatment) values (analyzed by ANOVA one way)

b non-significantly difference (P<0.05) as compared with control group values (analyzed by. ANOVA two way).

Table 2 : Effect of treatment with group 1 (Melatonin 5mg daily) on attacks frequency in patients with common migraine headache and group 2 (Propranolol 40 mg twice daily) as control group, after 1,2 and 3 months of treatment.

Group no.	Frequency of attacks/last week			
	Before treatment	After 1 month	After 2 months	After 3 months

1 (n=21)	5.33±0.12	3.66±0.31 ab	3.52±0.36 ab	3.74±0.41 ab
2 (n=20)	5.15±0.07	3.55±0.18 a	3.15±0.19 a	3.05±0.23 a

values are presented as mean ± stander error of the mean SEM.

a significantly difference (P<0.05) as compared with baseline(before treatment) values (analyzed by ANOVA one way).

b non-significantly difference ((P ≥0.05) as compared with control group values (analyzed by ANOVA two way).

Table 3 : Effect of treatment with group 1 (Melatonin 5mg daily) and group 2 (Propranolol 40 mg twice daily as control group) on Serum Aspartate Aminotransferases (AST) level in patients with common migraine headache after 1,2 and 3 months of treatment .

Group no.	AST (U/L)			
	Before treatment	After 1 month	After 2 months	After 3 months
1 (n=21)	22.19± 0.56	21.59±0.65 a	21.76±0.60 a	22.42±0.67 a
2 (n=20)	22.35±0.67	21.90±0.67 a	21.40±0.70 a	22.25±0.76 a

Values as presented as mean ± stander error of mean SEM.

a significantly no difference (P≥0.05) as compared with baseline(before treatment) values. (analyzed by ANOVA one way).

Table 4 : Effect of treatment with group 1 (Melatonin 5mg daily)) and group 2 (Propranolol 40 mg twice daily as control group) on Serum Alanine Aminotransferases (ALT) level in patients with common migraine headache after 1, 2 and 3 months of treatment.

Group no.	ALT (u/l)			
	Before treatment	After 1 month	After 2 months	After 3 months

1 (n=21)	34.19±0.49	34.00±0.51 a	34.80±0.5 4 a	33.38±0.5 9 a
2 (n=20)	33.40±0.48	34.25±0.51 a	35.30±0.6 2 a	33.90±0.5 2 a

Values are presented as mean ± stander error of mean SEM.

a significantly no difference ($P \geq 0.05$) as compared with baseline(before treatment) values. (analyzed by ANOVA one way).

Table 5 : Effect of treatment with group 1 ((Melatonin 5mg daily)) and group 2 (Propranolol 40 mg twice daily as control group) on Serum creatinine level in patients with common migraine headache after 1,2 and 3 months of treatment.

Group no.	Serum creatinine (mg/dl)			
	Before treatment	After 1 month	After 2 months	After 3 months
1 (n=21)	0.87±0.05	0.90±0.05 a	0.87±0.05 a	0.92±0.05 a
2 (n=20)	0.95±0.04	0.88±0.05 a	0.91±0.04 a	0.84±0.06 a

Value are presented as mean ± stander error of mean SEM.

a significantly no difference ($P \geq 0.05$) as compared with baseline(before treatment) values. (analyzed by ANOVA one way).