J Biochem Tech (2018) Special Issue (2): 98-101
ISSN: 0974-2328

# Investigating the Effectiveness of Silymarin in Treatment of Migraine Patients Referred to Medical Centers Affiliated to Arak University of Medical Sciences

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Received: 16 April 2018 / Received in revised form: 30 July 2018, Accepted: 02 August 2018, Published online: 05 September 2018


## Abstract

**Background and Objective:** Silybum marianum is one of the herbs which has been used in various studies. Therefore, this study aimed at investigating the effectiveness of Silymarin in relieving symptoms of migraine patients. **Materials and Methods:** In this study, 50 migraine patients diagnosed based on IHS scale and physician's diagnosis were randomly assigned into two groups of intervention and control. For the intervention group, one 70mg Livergol tablet was administered per day in addition to the standard treatment (propranolol and nortriptyline), while the control group tow received the standard treatment. One and two months after initiation of the treatment, pain severity and disability in the patients was evaluated using Migraine Disability Assessment and Visual Analogue Scale questionnaires. The data were analyzed using SPSS and through independent t-test and repeated measure test. **Findings:** Average age of the participants in the intervention group was 38.16 ± 8.8 years and in the control group, 39 ± 12.24 years. Independent t-test showed that there was no significant difference between the control and intervention groups in terms of the main variables of the study (P>0.05). Repeated measure test showed that one and two months after the intervention, there was a significant difference between the control and intervention groups in the mean scores of pain severity and disability and also among the three measurements so that pain severity and disability were reduced and they were lower in the intervention group than those in the control group (P<0.001). **Conclusion:** Considering the results of this study, Silymarin can be used as a supplement in treatment of the migraine patients as it contains powerful antioxidants and does not have important side effects.

**Keyword:** Pain, Silymarin, Migraine

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## Introduction

Migraine is one of the most prevalent types of headache in the world, including Iran, which affects 12% of the general population (Alaee and et al, 2013). Migraine affects women three times more than men. This disease is a neurovascular disorder related to the brain parenchyma which is disabling, progressive and chronic and has important effects on the lives of the patients (Sadeghi and et al, 2014). The majority of problems and costs due to headache are related to disability, pain and suffering and reduced quality of life (Alp and et al, 2010). Molecular mechanism of migraine is not completely known yet. It is believed that oxidative stress plays a role in pathology of migraine. The studies have shown that in migraine patients, the level of antioxidants decreases and total level of oxidants and oxidative stress index increases (Amery and et al, 1988). Also, various studies have shown that migraine and cluster headaches are associated with P450 enzyme deficiency (Hadinia and et al, 2010; Kusumi and et al, 2003). At present, various drugs are used for treating and preventing migraine. Drugs belonged to the category of triptan, ergot, β-blockers, sodium channel blockers, anti-seizures, tricyclic antidepressants and serotonergic agents are among these medicines. Most of these drugs have multiple side effects, especially ovarian cysts, obesity, liver complications and damages during pregnancy (Sadeghi and et al, 2014).

The studies have shown that Silymarin contains high amount of polyphenolic antioxidants and has supporting effects on neurodegenerative diseases (Roghani and et al, 2012). Silymarin, which is a bioflavonoid derived from the seed of Silybum marianum, is a hepatoprotective agent and its lower toxicity, powerful antioxidants, desired pharmacokinetic, detoxification, preventive, protective and cellular restoration properties and placebo-like side effects has made this herbal drug a healthy and appropriate medical agent. This drug has been used in various studies for treating Alzheimer's disease, Parkinson's disease, sepsis, burns, osteoporosis, diabetes, biliary diseases,

hypercholesterolemia and depression in human and animal models. Its neuroprotective, cardioprotective and renal protective properties in various damages have made Silymarin a powerful antioxidant (Baluchnejadmojarad and et al, 2011; Milić and et al, 2013). Neuroinflammation is an important factor in deteriorating brain damage. Silymarin is effective in preventing these damages through inhibiting neuroinflammation (Nassuato and et al, 1991). Additionally, Silymarin inhibits brain damage resulted from blood clots in cerebral arteries (Rui and et al, 1990). Also, the effectiveness of Silymarin in enhancing neural conduction in neural chords of the diabetic patients has been approved. Silymarin has also antioxidant effects on human platelets and acts as an antioxidant and free radical scavenger in human hepatic and pulmonary microsomes which provides protection against lipid peroxidation induced by chemicals (Locher and et al, 1998). However, this drug has not been used in treatment of migraine yet. Therefore, considering high prevalence of migraine in general population and its undesired consequences such as reduced quality of life and absence from work and the importance of using a safe drug for preventing migraine, especially in women who are affected by this disease more than men and can be at their productive age and most of the anti-migraine drugs have adverse side effects during pregnancy, Silymarin can be a supplement that not only has no hepatic side effects but also is not forbidden to be taken during pregnancy. Silymarin is a healthy herbal drug with the minimum side effects which has not been used in treatment of migraine so far. Therefore, this study aimed at investigating the effectiveness of Silymarin in relieving symptoms of migraine in a clinical trial bearing the code N12016022026667.

## Methodology

This study was a double-blind study conducted on the migraine patients suffering from this disease for at least 6 months and experiencing at least three headache attacks per month. After acquiring the permit from the Research Committee of Arak University of Medical Sciences bearing the ethics code IR.ARAKMU.REC.1394.282, the patients referring to Kosar Medical Center were included in the study based on the following inclusion criteria: suffering from migraine for 6 months, experiencing at least three headache attacks per month, being at the age range of 15-65 years and not following prophylaxis medication. They were allowed to leave the study if they were reluctant to continue. Then, they were examined by the neurologist and based on the criteria of international headache society (IHS) to be accurately diagnosed by migraine. After initial examinations, the patients were assigned to the intervention group or control group every other one. For the intervention group, 70mg Livergol was administered twice per day in addition to the standard treatment (10mg propranolol and 10mg nortriptyline per day), while the control group received the placebo, which was not different from Livergol in terms of form and shape, in addition to the standard treatment. The data collection tools were two questionnaires of migraine disability assessment (MIDAS) and visual analogue scale (VAS). VAS is a pain scale as a horizontal line graded from 0 to 10 on which 0 indicates “no pain” and 10 shows “worst pain imaginable”. VAS was invented in 1975 by Milzac, was tested in multiple studies since then and today, it is known as one of the most popular pain scales (Kelly, 2001). Migraine disability assessment (MIDAS) questionnaire was designed by Stewart et al. (Sajadi-Nejad and et al, 2009). The questions on MIDAS are responded by “yes” (4 points), “sometimes” (2 points) and “no” (0). This scale measures emotional disability and functional disability caused by headache. The higher the score, the higher the level of experienced disability. Correlation coefficient of these subscales with the whole test was 0.79 and 0.91. The validity through split-half method was obtained as 0.77 and Chronbach’s alpha for the whole test, emotional component and functional component was calculated as 0.86, 0.68 and 0.83, respectively (DeMaagd, 2008). So, the questionnaire, which has been used in different studies, enjoys the required validity and reliability. The questionnaires were filled in by a researcher asking the patients at the beginning of the study and 30 and 60 days after administration of the drug. The time period for including the patients in the study lasted for one year (from May 2016 to May 2017). The collected data were analyzed using SPSS and through statistical analysis.

## Results

50 migraine patients participated in this study. The participants were randomly assigned into two groups of control and intervention. There were 24 men and 26 women in the study and there was no significant difference between the two groups in terms of sex (P>0.05). Also, the age range of the participants was 16-63 years and there was no significant difference between the two groups in terms of age (P>0.05). Table 1 shows the demographic information.

Independent t-test showed that before the intervention, there was no statistically significant difference between the control and intervention groups in the main variables of the study (pain severity and disability) (P>0.05). Also, repeated measure test showed that there was a significant difference between the control and intervention groups in the average score of disability due to migraine (MIDAS) and mean score of pain severity based on VAS after each measurement (P<0.001). Tables 2 and 3.

**Table 1**. Demographic information

| Variable | | Intervention group | Control group | P value |
|---|---|---|---|---|
| Age | | 35.56±3.61 | 36.26±4.56 | .08 |
| Sex | Male | 7 | 9 | .09 |
| | Female | 18 | 16 | |
| Education | Higher education | 11 | 10 | 0.1 |
| | High school | 14 | 15 | |
| Marital status | Married | 12 | 13 | 0.27 |
| | Single | 13 | 12 | |
| Occupation | Employed | 10 | 9 | 0.4 |
| | Unemployed | 15 | 16 | |

**Table 2.** Mean and standard deviation of pain severity in the control and intervention groups after each measurement

| Variable | Group | No. | Mean | SD | Level of significance (independent t-test) |
|---|---|---|---|---|---|
| Pain severity before the intervention | Intervention | 25 | 7.60 | 1.93 | 0.156 |
| | Control | 25 | 8.32 | 1.57 | |
| | Total | 50 | 7.96 | 1.78 | |
| Pain severity after one month | Intervention | 25 | 5.80 | 2.73 | 0.001 |
| | Control | 25 | 7.28 | 1.54 | |
| | Total | 50 | 6.18 | 2.46 | |
| Pain severity after two months | Intervention | 25 | 4.16 | 2.30 | 0.001 |
| | Control | 25 | 6.32 | 1.51 | |
| | Total | 50 | 5.24 | 2.21 | |

**Table 3.** Mean and standard deviation of disability in the control and intervention groups in after each measurement

| Variable | Group | No. | Mean | SD | Level of significance (independent t-test) |
|---|---|---|---|---|---|
| Disability before the intervention | Intervention | 25 | 42.36 | 4.87 | 0.195 |
| | Control | 25 | 58.76 | 3.88 | |
| | Total | 50 | 50.56 | 4.44 | |
| Disability after one month | Intervention | 25 | 14.56 | 2.55 | 0.001 |
| | Control | 25 | 47.40 | 3.08 | |
| | Total | 50 | 30.98 | 3.25 | |
| Disability after two months | Intervention | 25 | 5.88 | 1.57 | 0.001 |
| | Control | 25 | 35.28 | 2.18 | |
| | Total | 50 | 20.58 | 2.4 | |

## Discussion

In this study, 25 participants were included in the intervention group with the average age of 39±12.24 years and 25 participants to the control group with average age of 38.16±8.8 years. Most of the participants in the study were women (84%) which is compatible with the approved higher prevalence of this disease in women (Sadeghi and et al, 2014). Also, most of the participants were married and housewife and had a high school diploma. Also, Independent t-test showed that before the intervention, there was no statistically significant difference between the control and intervention groups in the main variables of the study (pain severity and disability) (P>0.05).

The results of the study showed that there was a significant difference between the control and intervention groups in the mean score of disability due to migraine (MIDAS) and mean score of pain severity based on VAS after each measurement. Also, post-hoc test showed that this difference was present among the three groups. Additionally, independent t-test showed that there was a significant difference between the control and intervention groups in the mean pain severity and mean disability one and two months after the intervention so that pain severity and disability were reduced and they were lower in the intervention group than those in the control group. Therefore, based on the results of this study, Silymarin can relieve and reduce the severity of pain and disability caused by migraine in patients with migraine.

Molecular mechanism of migraine is not completely known yet. It is believed that oxidative stress plays a role in pathology of migraine. The studies have shown that in migraine patients, the level of antioxidants decreases and total level of oxidants and oxidative stress index increases (Amery and et al, 1988).

Silybum marianum, which is also known as cardus marianus, milk thistle fruit and akub, grows in many parts of Iran. The fruit and seed of this plant have been long used for treating disorders related to liver, bile ducts and gallbladder. Medical effects of this plant is mainly due to presence of a group of flavonoids which is called Silymarin. Silymarin is a combination of various types of flavonoids which are insoluble in water and soluble in alcoholic compounds. The seed of Silybum marianum is a good source of 5 types of flavonoids including silichristine, silidianin, isosilibin, silibin and doxyfuline. In traditional medicine, Silybum marianum has been used as a herb with adrenergic, anti-allergic, anti-cancer, antidepressant, antitoxic, anti-mycotoxin, anti-hepatotoxicity, anti-inflammatory, antileukotriene, antioxidant, antiprostaglandin, antivirus and heaptoprotective properties and an agent which causes healthy perspiration, helps digestion, lowers the level of blood lipids and cholesterol, acts as a sympatholytic agent, inhibits cAMP-phosphodiesterase synthesis, secrets glutathione, reduces the bile volume and treats fatty liver (Barnes and et al, 2007).

The study of Kittur et al. showed that Silybum marianum extract can increase nerve growth factor (NGF) and protect neurons against oxidative stress in laboratory conditions (Kittur and et al, 2002). On the other hand, other studies have shown that in migraine patients, the level of antioxidants is lower than that in healthy people and as Silymarin is a powerful antioxidant, it can be used in treatment of these diseases (He and et al, 2004). Also, Marrongelle et al. found in their study that Silymarin is one of the compounds that can be effective in preventing migraine along with other herbal compounds (Marrongelle & Staverosky 2003).

Kumar et al. also suggest that Silymarin can reduce the progress of neurodegenerative diseases such as Alzheimer's disease in laboratory models and this can be due to increase in resistance to oxidative stress (Kumar and et al, 2015).

Being safe, having the minimum drug interactions and containing powerful sources of flavonoids and antioxidants, Silymarin has gained considerable attention (Barnes and et al, 2007). Also, this drug's lower toxicity, powerful antioxidants, desired pharmacokinetic, detoxification, preventive, protective and cellular restoration properties and placebo-like side effects has made it a healthy and appropriate medical agent. The medical properties of this herb and its compounds have been employed in various studies for treating Alzheimer's disease, Parkinson's disease, sepsis, burns, osteoporosis, diabetes, biliary diseases, hypercholesterolemia and cancer. Silymarin is known as

a neuroprotective, cardioprotective and renal protective agent in damages with various pathologies and a powerful antioxidant (Milic and et al, 2013).

## Conclusion

Considering the results of this study, Silymarin can be used as a supplement in treatment of the migraine patients as it contains powerful antioxidants and does not have important side effects.

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