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Effectiveness of Oral Magnesium on Clinical Outcomes of Meningitis Patients at Dr. Mohammad Hoesin General Hospital Palembang

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ABSTRACT

Meningitis is an infection of the meninges that has high mortality and morbidity. Magnesium is an enzyme co-factor that plays a role in cellular physiology. Administration of magnesium has a neuroprotective effect that potential to improve the clinical outcome of meningitis patients. An experimental knowing the effectiveness of oral magnesium on clinical outcomes in meningitis patients at RSUP Dr. Mohammad Hoesin General Hospital Palembang and this is a randomized control trial (RCT) using the add-on and double-blind method in meningitis patients by measuring the Bartel Index (BI) and Modified Rankin Scale (MRS) scales at RSMH for the period 1 September 2022 – 30 November 2022. There were 30 meningitis patients, 13 patients (43.3%) were dominated by tuberculous meningitis, and another types of meningitis were bacterial meningitis, cryptococcal/fungal meningitis and viral meningitis for 11 patients (36.7%), 4 patients (13, 3%) and 2 patients (6.7%) with female sex 16 patients (53.3%) and male 14 patients (46.7%). The difference of value between BI and MRS, the magnesium group is better than the placebo group with a comparison value of 49,333 and 45.33 for the Bartel Index and comparison value of 2,867 and 2,533 for the modified rankin scale. However, this difference was not statistically different with p value > 0.05. The conclusion is there was an increase in BI and MRS values in both the placebo and magnesium groups with the increase in BI and MRS values being higher in the magnesium group.

1. Introduction

Meningitis is an infection of the meninges lining which can be caused by various kinds such as bacteria, viruses and fungi. Meningitis is a disease in the field of neurology that has a high mortality and morbidity. In 2003-2007 in the United States there were approximately 4100 cases of bacterial meningitis per year. In 2003-2004, of the 1670 cases of bacterial meningitis reported by the United States Emerging Infection Program, there were deaths in 13.0% of cases, with the most cases in adults being bacterial meningitis caused by S. pneumoniae of 88.9%. In developing countries like Indonesia, in 2009-2016 inpatients at Hasan Sadikin Hospital in Bandung, it was found that tuberculous meningitis (TBM) was the most common disease, accounting for 80% of all cases of central nervous system infection. In the period 2017 to 2020 at the Mohammad Hoesin Hospital, most meningitis was dominated by tuberculous meningitis (48%) followed by bacterial meningitis (30.4%), viral meningitis (19.6%) and cryptococcal (2%) with every 50% of patients has a clinical outcome in the form of sequelae. Meanwhile, the highest distribution of neurological clinical symptoms in meningitis patients was hemiparesis and fever, with the highest mortality rate occurring in

patients with a Glasgow Coma Scale (GCS) value of less than 11.[1,2,3]

Magnesium (Mg) is an enzyme co-factor that plays a role in regulating various biochemical reactions that are important for various physiological, cellular, and biochemical functions. There are more than 300 enzymes in the human body that are affected by magnesium. Magnesium is useful for maintaining muscle, nerve function, heart rhythm, bone strength and the immune system, while in cellular activity magnesium is involved in homeostasis such as sodium, potassium and calcium, as well as in the process of formation, transfer, storage and utilization of adenosine triphosphate (ATP), as the main energy source. The daily requirement of magnesium in adults is 300-420 mg per day which is obtained from daily nutritional intake in the form of nuts, vegetables, fruits, meat.[4,5]

In a prospective study of systemic infection regarding levels of inflammatory markers, it was found that magnesium intake was inversely associated with levels of hs-CRP, fibrinogen and IL-6. These findings provide evidence that dietary magnesium is beneficial on inflammatory markers. Magnesium also plays an important role in homeostatic regulation in Traumatic Brain Injury (TBI) events, magnesium acts as a non-competitive inhibitor of the N-Methyl-D-Aspartic Acid (NMDA) receptor which regulates calcium influx. In cases of TBI, there is a depletion of magnesium levels resulting in disruption of homeostatic control of NMDA receptors, causing a large influx of calcium and causing degeneration of neurons resulting in cell death. Therapy using magnesium sulfate can reduce post-TBI oxidative stress. Magnesium sulfate is a cerebral vasodilator that acts as an antagonist of calcium channels located in smooth muscle cells of blood vessels and has an effect on myosin-binding proteins, this regulates muscle contractions so that magnesium sulfate can increase cerebral perfusion. Magnesium sulfate has significant effectiveness against vasculitis and has a neuroprotective role because it can reduce the morbidity associated with cerebral infarction secondary to meningitis. There are statistically significant changes in the Bartel Index (BI) and modified rankin scale (MRS).[6,7,8]

Based on this background, researchers see the potential importance of magnesium in the process of Traumatic Brain Injury (TBI) events, affecting the incidence of systemic infection and clinical improvement of TB meningitis, but there is no previous research data regarding magnesium in the wider scope of meningitis etiology. Therefore the authors wish to examine the use of oral magnesium 1000 mg in all types of meningitis, whether in the form of bacterial, TB, viral or cryptococcal by assessing the effectiveness of oral magnesium on clinical outcomes using the Barthel Index and the modified rankin scale in meningitis patients in the inpatient installation of Dr. Moh. Hoesin General Hospital, Palembang.

2. Methods

This research is a randomized control trial (RCT) experimental study with the Add On method which was carried out in a double blind manner. The research was conducted at Dr. Mohammad Hoesin Palembang. The research is expected to take place from September 2022 – November 2022 or until the specified number of samples is met. The population in this study were meningitis patients who were hospitalized at Dr.Moh. Hoesin Palembang. While the sample of this study is part of the population that meets the inclusion criteria. The sample size was calculated using a pilot study approach where the minimum sample size to be analyzed was 30 samples consisting of 15 samples for the treatment group and 15 samples for the placebo group. All subjects who met the inclusion criteria were taken sequentially as a sample (consecutive sampling). Research subjects were pre-randomized to enter into groups with treatment or without treatment. Sampling was carried out until the number of samples was met with

the exclusion criteria of patients with serum magnesium levels > 2.4 mg/dL and patients who were not willing to participate in the study.

3. Results

In the period September – November 2022 a total of 41 meningitis/meningoencephalitis patients were found overall, both bacterial, TB, viral and cryptococcal/fungal treated at Dr. Mohammad Hoesin Palembang, but only 34 subjects met the inclusion criteria. Over time, there were 4 subjects who died before the research was completed, so that only 30 subjects underwent data processing.

Total of 30 patients who met the inclusion criteria in the period September-November 2022. There were 14 male patients and 16 female patients. Bacterial meningitis was found in 11 patients (36.7%), TB meningitis in 13 patients (43.2%), viral meningitis in 2 patients (6.7%) and cryptococcal meningitis in 4 patients (13.3%). The distribution of patients with the age group of 18-30 years was 12 patients (40%), the age group of 31-60 years was 14 patients (46.7%) and the age group >60 years was 4 patients (13.3%). The following presents general characteristics in Table 1.

Table 1. General characteristics of research subjects.

Characteristics	Frequency	Percentage
Age		
18 – 30 years	12	40 %
31 –60 years	14	46,7 %
> 60 years	4	13,3 %
Gender		
Male	14	46,7 %
Female	16	53,3 %
Meningitis type		
Bacterial	11	36,7 %
TB	13	43,3 %
Virus	2	6,7 %
Cryptococcus	4	13,3 %

Table 2 compares the values of the Barthel Index and the Modified Rankin Scale on the first day (before therapy) to after weekly therapy (7th to 14th day) in both groups. Prior to analysis, a data distribution test was performed using Shapiro Wilk and it was found that the data were normally distributed so that the data and analysis was carried out using an independent T-test.

In the modified ranking scale variable, days 1 - 7, the mean value before therapy in the treatment group was 4.80 ± 0.414 and after getting therapy on day 7 it was 3.13 ± 1.125 with a p-value = 0.000 while in the control group before therapy it was 4.47 ± 0.743 and on the 7th day of 3.53 ± 1.060 with a value of p = 0.000. Days 1 - 14, the mean value before therapy in the treatment group was 4.80 ± 0.414 and after receiving therapy on day 14 it was 1.93 ± 1.438 with a p value = 0.000 while in the control group before therapy it was 4.47 ± 0.743 and on day 3 14 of 1.93 ± 0.743 with a value of p = 0.000. From the comparison of the MRS scale, there was no difference in MRS values between the treatment and control groups.

Table 2. Comparison of the MRS scale before and after therapy in the treatment and control groups.

MRS	Treatment (Mg)		*p*	Control		*p*
	Before	After		Before	After	
Day 1 – 7	4.80 ± 0.414	3.13 ± 1.125	0.000	4.47 ± 0.743	3.53 ± 1.060	0.000
Day 1– 14	4.80 ± 0.414	1.93 ± 1.438	0.000	4.47 ± 0.743	1.93 ± 0.743	0.000

*Dependent t-test.

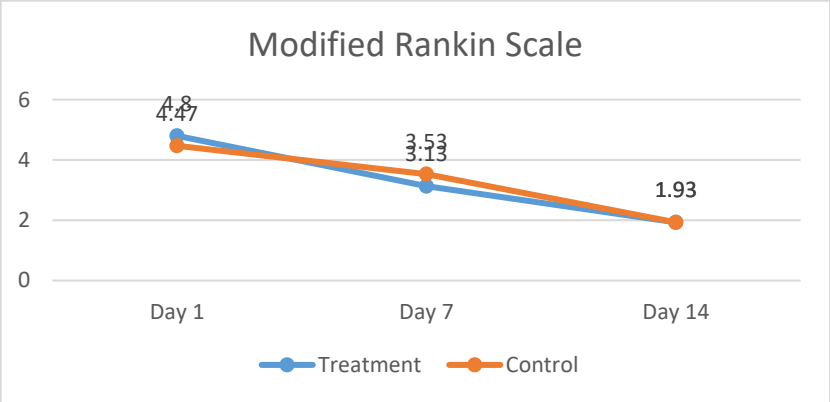

Figure 1. Comparison of the MRS scale before and after therapy in treatment and control groups.

In the Barthel Index variable, days 1 - 7, the mean value before therapy in the treatment group was 26.67 ± 17,895, and after receiving therapy on day 7, it was 62.33 ± 21,619 with a value of p = 0.000, while in the control group before therapy it was 36.00 ± 24,727 and on the 7th day of 57.00 ± 21.112 with a value of p = 0.000. Days 1 - 14, the mean value before treatment in the treatment group was 26.67 ± 17,895, and after receiving therapy on day 14, it was 76.00 ± 28,611 with a value of p = 0.000 while in the control group before treatment, it was 36.00 ± 24,727 and on day 3 14 of 81.33 ± 14.326 with a value of p = 0.000. From the comparison of the BI scales, there was no difference in the BI values between the treatment and control groups.

Table 3. Comparison of the BI scale before and after therapy in the treatment and control groups.

BI	Treatment (Mg)		*p*	Control		*p*
	Before	After		Before	After	
Day 1 – 7	26.67 ± 17.895	62.33 ± 21.619	0.000	36.00 ± 24.727	57.00 ± 21.112	0.000
Day 1 – 14	26.67 ± 17.895	76.00 ± 28.611	0.000	36.00 ± 24.727	81.33 ± 14.326	0.000

*Dependent t-test.

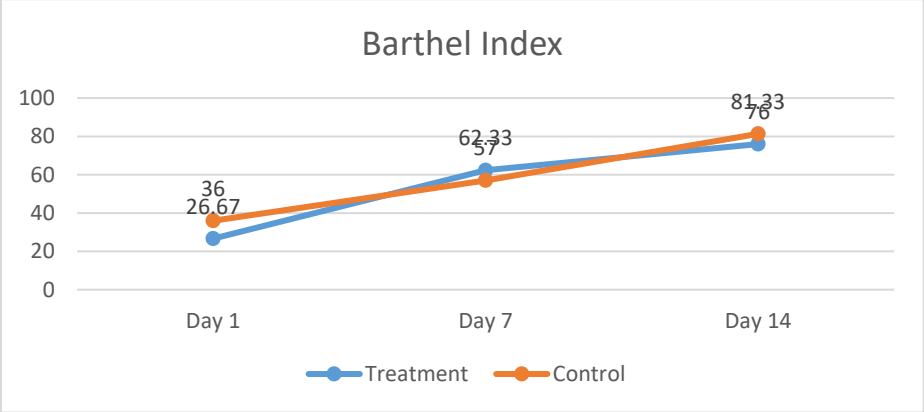

Figure 2. Comparison of the BI scale before and after therapy in treatment and control groups.

Comparison of the effectiveness of magnesium and placebo

In Table 4, a comparison is made of the difference in the MRS and BI scales in the treatment group and the control group. Prior to analysis, a data distribution test was performed using the Shapiro-Wilk, and it was found that the data was normally distributed ($p>0.05$) so that the data was presented in the mean value and analyzed using the Independent T-test.

Table 4. Comparison of the difference between MRS and BI before and after therapy in the treatment and control groups.

Scale	Treatment (Mg) Mean ± SD	Control Mean ± SD	p
BI	49.333 ± 22.028	45.333 ± 19.591	0.603
MRS	-2.867 ± 1.356	-2.533 ± 0.915	0.437

*Independent t-test.

From the above data by looking at the difference between BI and MRS, the group that received magnesium therapy was better than the group that received a placebo with a comparison value of the treatment group and the control group of 49,333 and 45.33 for the Bartel Index and a comparison value of 2,867 and 2,533 for the Modified Rankin Scale. However, this difference is not statistically different with a p value > 0.05.

In Table 5, a comparison is made of the difference in GCS before and after therapy in the treatment group and the control group. Prior to analysis, the data distribution was tested using the Shapiro-Wilk, and it was found that the data were not normally distributed ($p<0.05$) so that the data were presented in the average value and analyzed using the Mann Whitney test. There was no significant difference in the difference in GCS in the treatment group and the control group ($p>0.05$).

Table 5. Comparison of the difference in GCS before and after therapy in the treatment and control groups.

Scale	Treatment (Mg) median (min-max)	Control median (min-max)	p
GCS	5.00 (1-7)	5.00 (1-7)	0.446

*Mann-Whitney.

4. Discussion

On the modified ranking scale variable, on day 1 the mean value was obtained in Group A (control group) of 4.47 and the mean value in Group B (magnesium group) was 4.80 with a P value of 0.06, on the 7th day the mean value was obtained in Group A (control group) was 3.53 and the mean value in Group B (magnesium group) was 3.13 with a p value of 0.599 and on day 14 the mean value was obtained in Group A (control group) of 1.93 and the mean value in Group B (control group) magnesium) of 1.93 with a p value of 0.316 ($p > 0.05$) so it can be concluded that on days 1, 7 and 14 there was no significant difference in MRS values between the treatment and control groups.

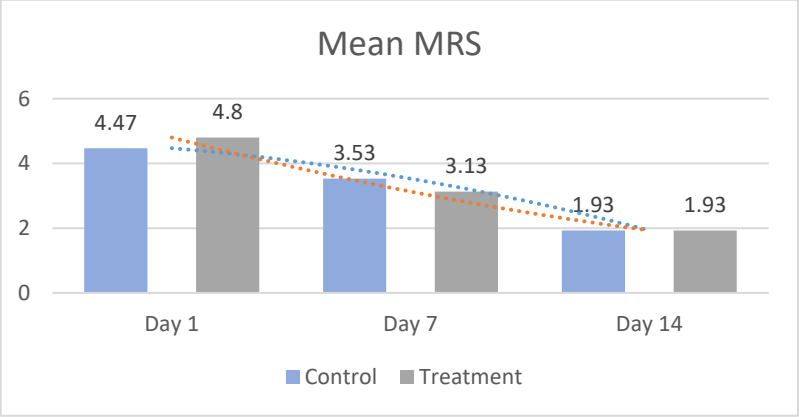

Figure 3. Graph of average values based on MRS.

In the Barthel Index variable, on day 1 the mean value was obtained in Group A (control group) of 36.00 and the mean value in Group B (magnesium group) was 26.67 with a p value of 0.246, on the 7th day the mean value was obtained in Group A (control group) was 57.00 and the mean value in Group B (magnesium group) was 62.33 with a p value of 0.500 and on the 14th day the mean value was obtained in Group A (control group) of 81.33 and the mean value in Group B (magnesium group) was 76.00 with a p value of 0.524 ($p > 0.05$) so it can be concluded that on days 1, 7 and 14 there was no significant difference in BI values between the treatment and control groups.

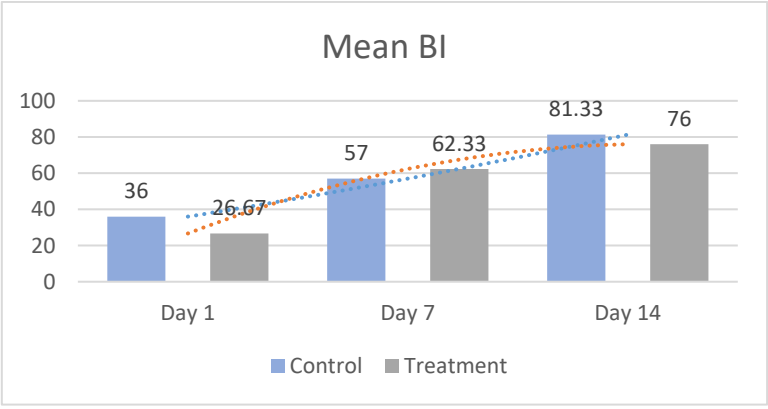

Figure 4. Graph of average values based on BI.

Based on these values, both the placebo group and the magnesium group experienced clinical improvement based on the Barthel Index and the Modified Rankin Scale. However, this mean value cannot be used as a reference for assessing which group is better because the BI and MRS values at the start of the measurement are not the same, so a uniform baseline value is not obtained. It should be remembered that this study was a study using add-on magnesium and at the same time patients were still receiving standard therapy. This means that clinically the comparison of values between the 2 groups is equally effective using only standard therapy by looking at the mean value of each group on day 7 and day 14. Figure 5 shows that there are differences in changes in the average MRS value on days 1-7 in the control and treatment groups. The mean value of group A (control group) on days 1-7 was 0.933 and group B (magnesium group) was 1.667. Meanwhile, if we compare the values from the beginning of the study to the final observation using the Modified Rankin Scale tool, the mean value of group A (control group) on days 1-14 is 2,533 and group B (magnesium group) is 2,867 statistically significant with a value of p = 0.000 (p<0.05).

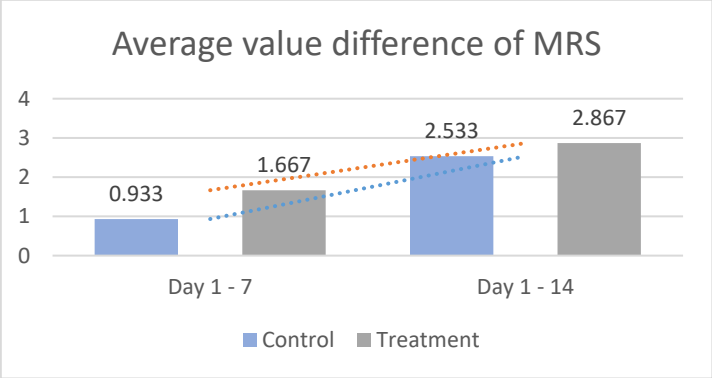

Figure 5. Graph of changes in the average value based on MRS.

Figure 6 shows that there are differences in the average BI values on days 1-7 in the control and treatment groups. The mean value of group A (control group) on days 1-7 was -21,000 and group B (magnesium group) was -35,667. Meanwhile, if we compare the values from the beginning of the study to the final observation with the Bartel Index tools, the mean change in group A (control group) on days 1-14 is -45,333 and group B (magnesium group) is -49,333 statistically significant with a p value =0.000 (p<0.05).

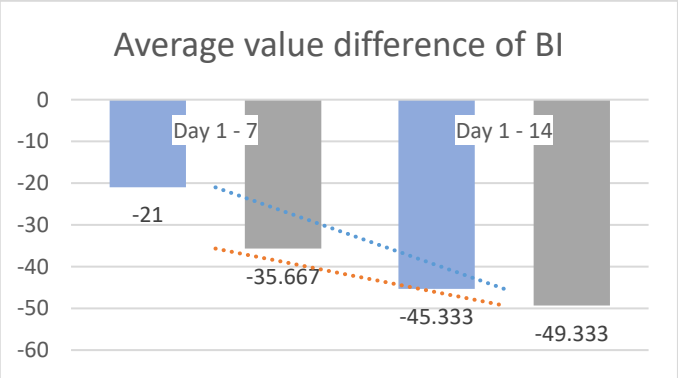

Figure 6. Graph of Changes in the average value based on BI.

From the data above by looking at the mean changes in BI and MRS, magnesium is actually better than the group that received a placebo with a comparison value of Group A and Group B of -45.33 and -49.333 for the Bartel Index and a comparison value of 2.533 and 2.867 for the Modified Rankin Scale. It's just that the difference in value in the two groups is not too far away. So it cannot be concluded that Magnesium is truly superior and can be routinely recommended for patients with meningitis.

Administration of magnesium has beneficial clinical outcomes demonstrating a clinically relevant correlation to administration of Mg2+ as a therapeutic agent in animal models of pneumococcal meningitis. This study shows that magnesium can prevent brain pathogenicity due to the neurotoxin PLY, which is released from S. pneumoniae, providing benefits in studies conducted in animal models with pneumococcal meningitis. The occurrence of cerebral edema contributes to the death of brain tissue through the mechanism of reducing blood flow to the brain, so that appropriate management is needed in conditions of acute cerebral edema. Cerebral edema conditions also play an important role in pneumococcal meningitis. Increased vascular permeability is thought to be a major factor in brain edema due to infectious processes. PLY can also cause intracellular edema so that it can increase tissue penetration by pathogenic bacteria, where this occurs due to the reorganization of astrocytes. The role of PLY as an important pathogenic factor in pneumococcal meningitis has been confirmed in many experimental and clinical studies. Reduced PLY is associated with a milder disease course and better clinical outcome. Other CDC toxin groups, such as perfringolysin and listeriolysin also have high virulence. In a study by Patonet et al. demonstrated that immunization with PLY can increase the survival rate of a mouse model infected with S. pneumoniae.[9,10,11]

Magnesium (Mg), chemical element, one of the alkaline earth metals Group 2 (IIa) of the periodic table, and the lightest structural metal. Its compounds are widely used in medicines and magnesium is one of the essential elements for all cellular life. Magnesium balance is regulated by the intestines, bones and kidneys. In general, magnesium is absorbed by passive paracellular mechanisms in the ileum and distal jejunum, while smaller amounts are actively transported in the large intestine. The balance is mainly regulated by the kidneys, about 95% of the excreted magnesium is reabsorbed. Oral absorption varies 20-50% of the oral dose absorbed by the body. The average body Mg2+ level is about 1000 mmol (20 mmol/kg body weight), of which 50% is in the soft tissue and the remainder in the bone. In clinical practice the serum magnesium concentration is the most commonly used test to assess magnesium status and the normal reference range is usually 0.7-1 mmol/L (equivalent to 1.5-2 mEq/L or 1.7-2.4 mg/L). dL. However, normal values vary from laboratory to laboratory, and various studies have used slightly different ranges up to 2.6 mg/dL.

Normal serum magnesium does not necessarily mean that the total body magnesium content is adequate because only less than 0.3% of total body magnesium is found in serum. The most commonly used and available method of assessing magnesium status is measurement of serum magnesium concentration, although serum levels have little correlation with total body magnesium levels or concentrations in specific tissues. Several conditions related to magnesium, including someone with heart problems and kidney problems. Where the kidneys are not functioning properly have difficulty clearing magnesium from the body. Patients with diabetes mellitus can also experience magnesium deficiency, because magnesium absorption is reduced. Likewise for someone who has a habit of drinking alcohol, because this condition can also cause magnesium

deficiency. In some people, magnesium can cause stomach pain, nausea, vomiting, diarrhea and other gastrointestinal disturbances. More serious conditions can occur such as low blood pressure, muscle weakness if consumed in very large quantities. Although generally rare, this condition is usually reported with impaired renal function.

In the comparison of the mean BI and MRS values in the two groups the results were not uniform. On the first day, the BI value was measured for the group receiving magnesium, which tended to be smaller than the placebo group. Meanwhile, the MRS value of the group that received magnesium tended to be greater than that of the placebo group. This could be due to the uneven distribution of the etiology of meningitis between the placebo and magnesium groups, resulting in varying BI and MRS values. In the group that received magnesium, the majority were TB meningitis patients, 7 patients, while the control group, the majority were bacterial meningitis patients, 6 patients. TB meningitis tends to have a more severe clinical course, resulting in lower BI values and greater MRS. Clinical improvement in TB meningitis tended to take longer than bacterial meningitis, this resulted in the mean MRS value in the placebo group and the magnesium group on day 14, even the mean BI value in the placebo group was better than the mean value in the magnesium group.

The limitation of this study was that the sample was not homogeneous, meaning that many factors and co-morbidities could affect the mean MRS and BI on the first day of measurement, so the values were not the same and the same baseline could not be obtained. In addition, researchers did not analyze the standard therapy given to patients, both the dose, duration of administration and other therapies that might affect the effectiveness of magnesium on clinical outcomes, this is because the etiology of meningitis in samples can vary. In addition, oral magnesium is also affected by absorption conditions. in the stomach and intestines where each patient has different conditions, it is necessary to carry out research and in-depth studies regarding the effectiveness of absorption of magnesium in the stomach, intestines whether oral magnesium administration affects blood magnesium levels (serum magnesium) or in further studies researchers can use different magnesium preparations such as via the intravenous route of administration. In this study the researchers also did not periodically check magnesium levels so that periodic magnesium levels were not known until after the observation was completed, this could be considered in further studies to monitor serum magnesium levels.

5. Conclusion

The incidence of meningitis at Dr. Mohammad Hoesin General Hospital in the period September to November 2022 was 41 patients. Of the 30 meningitis patients, 13 patients (43.3%) were mostly dominated by tuberculous meningitis, while other types of meningitis, namely bacterial meningitis, cryptococcal/fungal meningitis and viral meningitis, accounted for 11 patients (36.7%), 4 patients (13.3%) and 2 patients (6.7%). Meningitis patients were mostly female, 16 patients (53.3%) and 14 patients (46.7%) male. Meningitis patients based on meningitis etiology were generally found in the age category of 31-60 years in 7 patients (23.3%) for bacterial meningitis, while in the 18-30 year age category there were 6 patients (20%) for TB meningitis. There was an increase in BI and MRS values occurring in both the placebo and magnesium groups with the increase in BI and MRS values being higher in the magnesium group. Magnesium has the potential as an adjuvant therapy that can improve the clinical outcome of meningitis patients, but recommendations for giving magnesium as adjuvant therapy to meningitis patients require further research.

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