Original article

The effects of gabapentin on improvement of consciousness level in patients with traumatic brain injury: A randomized clinical trial

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BACKGROUND: Traumatic brain injury (TBI) is known as one of the most important causes of mortality in middle-aged population. The aim of this study was to evaluate the effects of gabapentin in improvement of consciousness level in these patients. **METHODS:** This randomized clinical trial was performed in March 2008 to September 2009. A total number of 60 patients from neurology clinics of Kashani Hospital (Isfahan, Iran) were randomly divided into two groups of 30 subjects as the case and control groups. The groups were respectively treated with 300 mg gabapentin and placebo twice a day for two weeks. The electroencephalogram (EEG), Glasgow Outcome Scale (GOS), and Glasgow Coma Scale (GCS) findings were evaluated in all patients before and one week after the intervention. **RESULTS:** The mean values of GCS and GOS before and after the treatment were not significantly different between the groups. This study showed significant changes in EEG patterns after treatment with gabapentin. **CONCLUSIONS:** Gabapentin might not be suggested for management of unconsciousness due to TBI.

KEYWORDS: Gabapentin, Brain Injuries, Consciousness, Electroencephalography

BACKGROUND

Traumatic brain injury (TBI) is known as one of the most important causes of mortality in middle age population. It is assumed as the third cause of mortality through the whole course of life. Although different rates of mortality due to these injuries have been reported, an estimated rate of 2.5 per 1000 persons each year would be acceptable. Car accidents are the major causes of TBI. In fact, over 65% deaths in accidents are due to TBI. Therefore, good information about the mechanism and physiopathology of TBIs are needed for correct diagnosis and treatment.[1,2]

Various medical regimens have been used to treat syndromes which happen after TBIs. In other words, there is no standard protocol of medical treatment some previous animal and human studies even suggested these treatments to possibly worsen the prognosis.[3]

Different studies have evaluated the effects of some medications on complications of TBIs such as loss of consciousness, as a major problem. They reported some drugs like alpha-2 agonists, antidepressants, antiepileptics, benzodiazepines, neuroleptics, opioids, and beta blockers to have some favorable effects.[4-7] On the other hand, dysautonomia is one of the other TBI complications whose pharmacological management in comatose patients due to TBI is very important. Some studies have shown that gabapentin may be useful in these patients.[4]

Gabapentin is a gamma aminobutyric acid (GABA) analogue whose exact mechanism of action is not known.[8] Among the several purposes that gabapentin is used for, treating seizures or pains is the most important. Some aspects of its mechanism of action is known especially in the field of pain controlling by having effects on GABA system through N-type Ca2+ channels but other parts are still unclear.[9-12] It may act by affecting the reticular activating system.

Not enough studies have assessed the effects of this drug in improving consciousness level of TBI patients. Therefore, the aim of this study was to evaluate the effects of gabapentin on consciousness according to their Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) scores and also electroencephalogram (EEG) results.

METHODS

Study population and design

In this double blind, randomized clinical trial, patients were recruited from neurosurgery and emergency divisions of Kashani Hospital (Isfahan,

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Iran) during March 2008 to September 2009.

The patients who suffered from moderate ($8 \leq GSC < 13$) and severe ($GCS < 8$) traumatic brain injury were included. Patients who died during the study, could not tolerate gabapentin or presented its severe side effects were excluded.

We calculated that a sample size of 60 patients was required to identify a difference of 1.5 in the GCS between groups, with $p < 0.05$ as the level of significance, and assuming a common standard deviation (SD) of 2 for gabapentin and placebo treatment groups.

After signing the written informed consents by their guardians, the patients underwent a complete test including complete physical examination and evaluation of GCS and GOS scores by an expert neurologist or neurosurgeon. An EEG was also recorded when the hemodynamic condition of the patient became stable.

Afterwards, the patients randomly received 300 mg gabapentin (Darou Darman Pars Co., Iran) or placebo (School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran) twice a day for two weeks. The randomization was performed by a computer generated list. The color and size and appearance of the drug and the placebo were matched. For unconscious patients, the drug was administered using a gavage.

During this period, the patients were followed and examined every day for probable problems or drug side effects. The consciousness level was also checked regularly. One, two, and three weeks after beginning the treatment, GCS and GOS scores were determined and EEG was repeated.

The EEG results were divided into two groups of normal and abnormal. The abnormal findings included asymmetry, focal slow waves or diffuse slow waves.

This study evaluated the hypothesis that administrating 600 mg/day gabapentin would probably improve consciousness level of TBI patients according to parameters like GCS and GOS and EEG results.

Ethical considerations

The Ethics Committee of Isfahan University of Medical Sciences (Isfahan, Iran) approved the study. This clinical trial was also registered in the Iranian Registry of Clinical Trials (IRCT) as IRCT201009204786N1.
In addition, the guardians of all patients provided written informed consents.

Assessment methods

EEG: The EEGs were recorded by Scan L T EEG system (Compumedics Ltd., Australia). EEGs were recorded and analyzed by an expert neurologist who was blinded to the groupings. The results were reported as normal or abnormal.

GCS and GOS: GCS and GOS scores of patients were determined by a neurosurgeon who was blinded to the groupings.

Statistical analysis

Differences in GCS and GOS scores between the two groups of study were analyzed by independent-sample t-test. Chi-square test was also used to compare EEG results between groups. $SPSS_{16}$ for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

The demographic information

After offal exclusions, 60 TBI patients were enrolled in this study. The flow diagram of patients is shown in Figure 1. Males and females constituted 75% (n = 45) and 25% (n = 15) of the recruited patients, respectively. Since there were 24 and 21 males, 6 and 9 females in the case (gabapentin) and control (placebo) groups, respectively, the two groups were not significantly different in terms of gender (P = 0.57). The mean age of patients was 39.8 ± 18.8 years in the whole population, 41.1 ± 19.4 years in the case group, and 38.5 ± 18.6 years in the control group (P = 0.59).

The GCS and GOS data

The GCS and GOS data is summarized in Table 1. The differences between the two groups before and after the trial were not significant.

EEG

The prevalence of abnormal EEG findings was significantly different before and after the intervention in the case group. However, no significant difference was found between the values in the control group (Table 2).

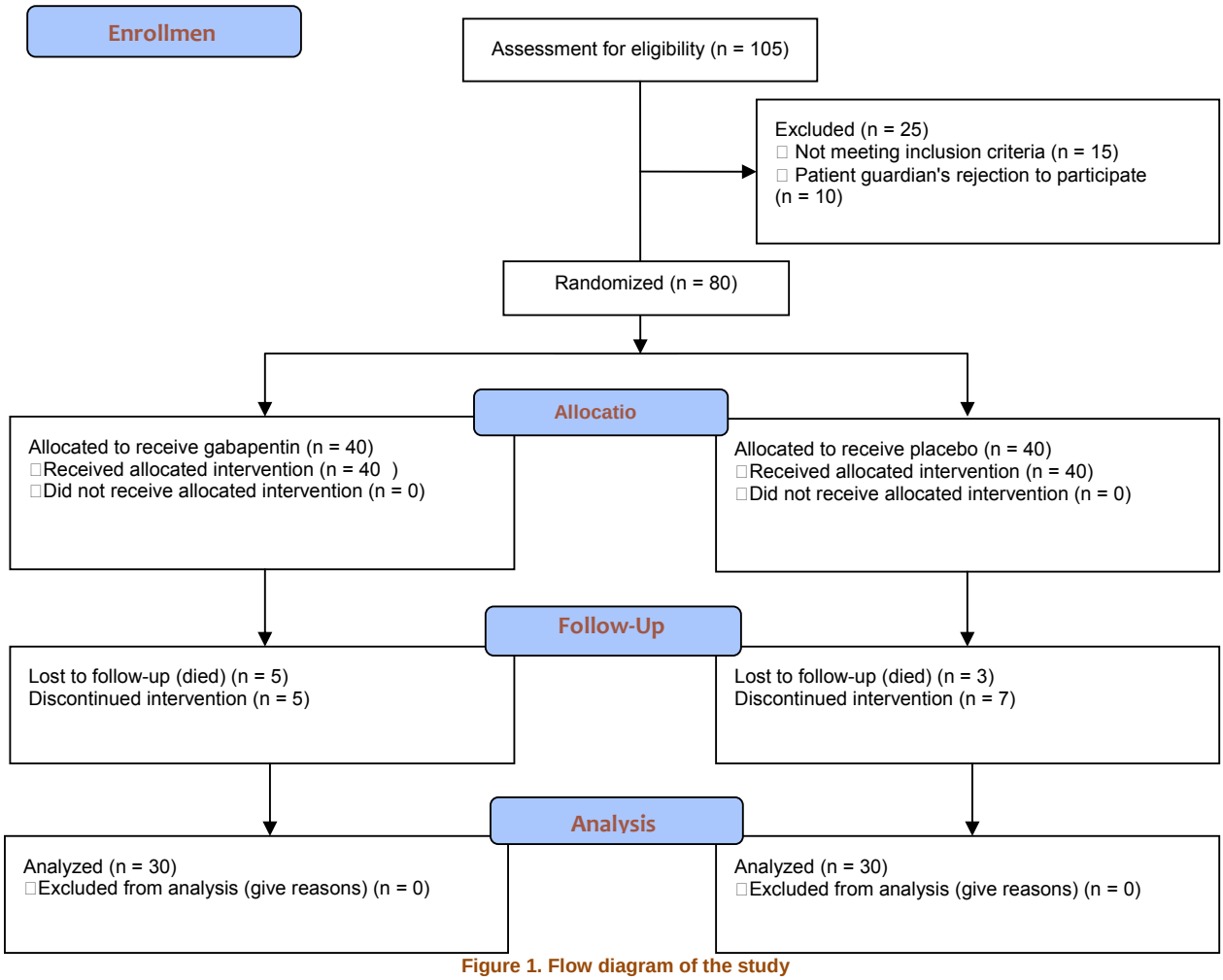

Figure 1. Flow diagram of the study

Table 1. Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) scores during the study

	Before intervention	At the 1st week	At the 2nd week	One week after the end of intervention	P-values within groups
GCS in the case group (3-15)	7.67 ± 4.1	9.17 ± 4.09	10.03 ± 4.37	10.87 ± 4.45	0.09
GCS in the control group (3-15)	8.40 ± 4.44	9.63 ± 4.16	10.33 ± 4.25	11.33 ± 4.38	0.13
Comparison between groups (P-value)	0.50	0.60	0.70	0.60	
GOS in the case group (1-5)	3.20 ± 0.55	3.57 ± 0.82	3.73 ± 0.94	3.70 ± 1.44	0.40
GOS in the control group (1-5)	3.33 ± 0.66	3.67 ± 0.88	3.67 ± 0.92	3.73 ± 1.48	0.60
Comparison between groups (P-value)	0.40	0.60	0.70	0.90	

The results are presented as mean ± SD.

Table 2. The prevalence of abnormal electroencephalogram (EEG) among the patients of both groups

	Before treatment	1 week after treatment	P-value
Gabapentin treated	17 (56.7%)	12 (40%)	0.04
Placebo treated	18 (60%)	16 (53.3%)	0.65
P-value	0.879	0.046	

DISCUSSION

This clinical trial assessed the effects of gabapentin on consciousness level of TBI patients. According to our results, the differences in GCS and GOS scores and EEG parameters before and after treatment were not significant. Gabapentin may thus not be useful for improving patients' conditions.

Gabapentin is an analogue of GABA which is used

for adjunctive therapy of partial and generalized seizures. It is also effective on neuropathic and spasmodic pains. Despite the close relationship between this drug and GABA, it does not seem to be effective on GABA receptor. However, it may change the metabolism or release of GABA.

Although the dosage of this medication ranges from 600 to 4800 mg daily, there is not enough information about the effectiveness and tolerability of different doses.[4-6,8] Since higher doses of this drug may cause more reduction in the consciousness level of patients, we preferred to use the lower dose in TBI patients.

On the other hand, according to previous studies, gabapentin is more useful in seizure attacks and spasticity of TBI patients.[13-15] There have though not been sufficient studies about the effects of gabapentin on consciousness. This study may thus be one of the first investigations in this field.

EEG is a useful tool for evaluation of brain cortical function and can be used for prognosis determination.[16] Changes in EEG patterns are associated with recovery of consciousness. This study showed significant changes in EEG patterns after treatment with gabapentin. The GCS scores of the patients improved, but not significantly, with gabapentin which could affect the EEG patterns.

Using of antiepileptic drugs for the first seizure, especially about post-traumatic seizures, could prevent the secondary seizures.[17]

According to some studies, gabapentin may have a function in controlling injury depolarizations in stroke and TBI.[18]

The limitations of this study could be summarized as using a low dose of gabapentin and short term follow-up of patients.

In conclusion, gabapentin might not be suggested for management of unconsciousness due to TBI, but it could probably be used for other TBI complications.

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