A comparative study of ketamine vs electroconvulsive therapy in the management of major depressive disorder

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Received 29 February 2020
Revised 19 March 2020
Accepted 28 March 2020
Published 30 September 2020

Menoufia Medical Journal 2020, 33:1088–1093

Objective

The aim was to investigate the efficacy of ketamine vs electroconvulsive therapy (ECT) in hospitalized patients suffering from treatment-resistant major depressive disorder (MDD).

Background

Both propofol and ketamine are the commonly used anesthetic agents, but recent clinical studies have suggested that ketamine has rapid-acting antidepressant properties, itself, at subanesthetic doses.

Patients and methods

A clinical comparative randomized cross-sectional study was conducted on 20 patients suffering from treatment-resistant MDD, and receiving ketamine only (group 1) and 20 patients suffering from treatment-resistant MDD receiving ECT only (group 2), who were recruited from inpatients wards of Neuropsychiatry Department, Menoufia University and Met-Khalaf Hospital for Psychiatric Health from December 1, 2018 until March 14, 2019. All participates were subjected to full detailed general medical, neurological, and psychiatric history and examination.

Results

There was a statistically insignificant differences between the studied patients regarding the types of depression ($P = 0.61$). Bipolar depression and MDDs were represented in 57 and 54% in the ECT group and 43 and 46% in the Ketamine group, respectively. Also, catatonic depression, melancholic subtype, and seasonal affective disorder were represented by 80, 66.7, and 100% in the Ketamine group vs 20, 33.3, and 0.00% in ECT group, respectively.

Conclusion

There was statistically significant difference between the ketamine group and ECT, regarding the efficacy of both ketamine and ECT in favor of the ketamine group as ketamine has a more rapid effect in improving depressive symptoms in MDD patients and have more rapid antidepressant effects compared with ECT.

Keywords:

antidepressant, electroconvulsive therapy, ketamine, major depressive disorder

Menoufia Med J 33:1088–1093

1110-2098

Introduction

Depressive disorders, including both major depressive disorder (MDD) and bipolar depression are severe and chronic psychiatric illnesses that are associated with substantial morbidity and high health-care costs, affecting ~350 million people worldwide each year [1]. The WHO has predicted that depression will become the second largest cause of disability worldwide by 2020, with its highest prevalence among adolescents [2]. Psychopharmacological treatments, psychotherapy, and electroconvulsive therapy (ECT) have all been widely used to treat MDD and bipolar depression. However, the Sequenced Treatment Alternatives to Relieve Depression study found that a majority of patients do not achieve clinical remission after the first treatment and many become treatment resistant [3].

With depression set to become the second largest cause of disability worldwide by 2020, it is important to examine carefully the cost effectiveness of any new treatment. Although over the past half century the biogenic amine models have provided meaningful links with the clinical phenomena of, and the pharmacological treatments currently employed in, mood disorders, there is still a need to examine the contribution of other systems to the neurobiology and treatment of mood disorders [4]. Current treatments for MDD are only partially effective in many cases and, in some cases, not at all effective. For instance, a large study on 3671 outpatients with MDD demonstrated that only 36% of MDD patients achieved remission following optimized trial of the selective serotonin reuptake inhibitor citalopram for up to 12 weeks [5]. Furthermore, remission in half of the patients

often occurs after 6 months of treatment with two antidepressant trials [3].

ECT had been demonstrated to be an effective therapy for MDD [6], with a response rate of ~79% and a remission rate of 75% [7]. There is some evidence that adequate seizure duration and higher doses of electricity are essential to optimize the antidepressant effects of this treatment [8]. Propofol is a commonly used sedative and anesthetic agent for ECT. However, it has potent anticonvulsant properties, and thus may impact the quality of the induced seizure and hamper the effectiveness of ECT treatment [9].

Ketamine is a commonly used intravenous anesthetic with a rapid and lasting antidepressant effect. In addition, it is currently used as an anesthetic in ECT. High-dose and repeated use of ketamine may lead to delirium as well as other psychiatric complications, while low-dose ketamine is safer and has the potential to enhance the efficacy of ECT in MDD patients [10]. In addition, current studies have confirmed that a single low dose of ketamine can maintain a long-term antidepressant effect, which can last for more than 7 days [11]. Based on this, the repeated administration pattern of ketamine in each ECT course has been challenged. However, it is not yet clear whether intermittent administration of ketamine can produce the same enhanced effects of ECT.

This study has been designed to investigate the efficacy of ketamine vs ECT in hospitalized patients with resistant MDD.

Patients and methods

A clinical comparative randomized cross-sectional study was conducted on 20 patients suffering from resistant MDD, and receiving ketamine only (group 1), and 20 patients suffering from resistant MDD, and receiving ECT only (group 2), who were recruited from inpatients wards of Neuropsychiatry Department, Menoufia University Hospital, Shebin-El Kom Teaching Hospital, and Met-Khalaf Hospital for Psychiatric Health, Menoufia, Egypt from December 1, 2018 until March 14, 2019. Ethical consideration: all participants signed a written informed consent that explained to them the objective of the study before the study started. Approval of the study protocol was obtained by Ethics and Scientific Committee of Menoufia University Hospital. Inclusion criterion: Both sexes aged between 18 and 75 years and diagnosed with resistant MDD according to Diagnostic and Statistical Manual of Mental Disorders (DSM-V) without psychotic features. Resistant MDD refers to inadequate response to at least one antidepressant trial of adequate doses and duration [12].

Exclusion criteria: patients with primary psychotic disorder, manic and hypomanic episode, mental retardation, dementia, and mood disorder due to general medical condition, and those with substance dependence or serious medical condition, fever, malignant diseases, and infectious diseases.

All the participants were subjected to detailed medical history and examination.

Participants who meet criteria for the diagnosis of MDD, currently in major depressive episode, according to DSM-V [12] as determined by a structured clinical interview by a psychiatrist. Psychometric studies: Beck depression inventory scale (BDI); BDI is a multiple-choice questionnaire that clinicians may use to rate the severity of a patient's major depression [13]. Scoring: method for scoring varies by version. For the BDI 21, a score of 0–9 is generally accepted to be within the normal range (or in clinical remission), while a score of 10–15 indicates mild severity; a score of 16–23 indicates moderate severity; a score of 24–36 indicates severe depression and a score of 37 and more indicates more severe depression which is usually required for entry into a clinical trial. The scale generally takes 5–10 min to complete [13]. Routine laboratory tests were renal function tests, liver function tests, complete blood count, and erythrocyte sedimentation rate. Description of the intervention: all patients were subjected to the first baseline BDI scale (self-reporting of symptoms) before the study (first BDI at December 1, 2018). Forty patients with DSM-IV MDD were divided in two groups which received either six intravenous infusions of ketamine hydrochloride (0.5 mg/kg 45 min) or six sessions of ECT (every 48 h). The patient was followed up by BDI scale 24 h after each treatment and 72 h and 1 week after last Ketamine injection or ECT session and then monthly for 3 consecutive months (until March 14, 2019 the end of the study). The patient is fasting for 8 h before the intervention. Thymatron DGX (Somatics INC, NY, USA) apparatus was used for ECT session, followed by injection of atropine (0.5 mg), followed by injection of the general anesthetic (thiopental Na 2–3 mg/kg), followed by injection of succinylcholine (0.5 mg, g), followed by application of the stimulus (sine wave) which was bitemporal, followed by induction of therapeutic seizures. ECT was applied to the patients in different frequencies ranging from 50 to 400 mv over different durations ranging from 4 to 5 s in six times every 48 h. Clinical assessment of remission was done by: first, BDI scale shows a reduction of

BDI scores to 0–9, which indicates no depression and second, also objectively by three items most frequently judged to be very important in determining remission were the presence of features of positive mental health such as optimism and self-confidence; a return to one's usual, normal self; and a return to usual level of functioning. Safety and side effects of the intervention (both Ketamine and ECT): both ketamine and ECT were well tolerated in all patients. Overall, there was no significant change in hemodynamic parameters including heart rate and blood pressure in both groups. There was only increase in systolic blood pressure as well as heart rate in three patients after the second and the third dose of ketamine, which was temporary and this rise was not clinically significant. In the ECT group, the hemodynamic parameters were not significantly altered. Considering the fact that intravenous administration of ketamine might have some unwanted effects on hemodynamic and cognitive function [14], some recent studies have shown that other routes of ketamine administration such as intranasal treatment or oral treatment [15,16] could be well tolerated and be effective in the treatment of mood disorders. Therefore, they could be a useful and easier way for long administration in MDD patients.

Statistical analysis

Results were analyzed and tabulated using Microsoft Excel 2016 (Albuquerque, New Mexico, U.S) and SPSS v. 21 (SPSS Inc., Chicago, Illinois, USA). Percentage, mean ± SD, and median were obtained. Analytical methods included χ^2, Student's, independent *t*-test, and one-way analysis of variance test. A value of *P* less than 0.05 was indicated to be statistically significant.

Results

In the studied population, the age of the studied group ranged from 18 to 75 years. In 11 (27.5%) patients the age was less than or equal to 40 years, followed by 10 (25%) patients in the age of less than or equal to 50 or 60 years (Table 1). In this study, there was statistically insignificant differences between the studied patients regarding sex (χ^2 = 0.752, *P* = 0.467) and age (χ^2 = 2.27, *P* = 0.051) (Table 2). In the current study, there was statistically insignificant differences between the studied patients regarding depression types (*P* = 0.061). Bipolar major depression and MDD were represented in 57 and 54% in the ECT group and by 43% and 46% in the ketamine group, respectively. Also, catatonic depression, melancholic subtype, and seasonal affective disorder were represented by 80, 66.7, and 100% in the ketamine group vs 20, 33.3, and 0.00% in the ECT group, respectively, (Table 2). In the current study, there was statistically significant difference between ketamine group and ECT regarding efficacy of both ketamine and ECT in favor of ketamine group as ketamine has a more rapid effect in improving depressive symptoms in MDD patients and have more rapid antidepressant effects compared with ECT. Also, we found that repeated treatments with low doses of ketamine (0.5 mg/kg, once every 48 h) and ECT can exert rapid antidepressant effects in patients with MDD. These data suggest that the antidepressant effects of ketamine are more rapid and effective ECT, in the early stages of treatment (Table 2). Because of violation of sphericity assumption, the Greenhouse–Geisser correction for the degree of freedom was used. Repeated one-way analysis of variance showed a statistically significant effect of the time on BDI score (*P* < 0.001). The difference in BDI score between ECT and ketamine group was statistically significant (*P* < 0.001). The interaction between time and group was also significant (*P* < 0.001), concluding that the difference in the effect of both ketamine and ECT on depression over the time was statistically significant (Table 3).

Table 1 Distribution of age categories among the studied patients

	Studied patients (*n*=40)		Cumulative %
	Frequency	%	
Age categories (years)			
20-≤30	9	22.5	22.5
≤40	11	27.5	50.0
≤50	10	25.0	75.0
≤60	10	25.0	100.0
Total	40	100.0	

Discussion

MDD is a prevalent and chronic disorder. The recurrence is one of the several forms of chronicity. Estimates indicate that 60–80% of adults who experience one episode will undergo at least one recurrence, with the majority of recurrences occurring within the first 5 years [17,18].

A clinical comparative randomized cross-sectional study was conducted on 20 patients suffering from resistant MDD and receiving ketamine only (group 1), and 20 patients suffering from resistant MDD and receiving ECT only (group 2), who were recruited from inpatient wards of Neuropsychiatry Department, Menoufia University Hospital, Shebin-El Kom Teaching Hospital and Met-Khalaf Hospital for Psychiatric Health, Menoufia, Egypt from December 1, 2018 until March 14, 2019.

Table 2 Comparison between ketamine and electroconvulsive therapy groups regarding sex, age categories, depression types, and Beck depression inventory score after treatment

Factors	Studied patients (*n*=40) [*n* (%)]		χ^2	Significance
	Ketamine (*n*=20)	ECT (*n*=20)		
Sex				
Male	10 (50)	11 (55)	0.752	0.467
Female	10 (50)	9 (45)		
Age (years)				
≤30	3 (15)	6 (30)	2.27	0.051
≤40	8 (40)	3 (15)		
≤50	3 (15)	7 (35)		
≤60	6 (30%)	4 (20%)		
Depression types				
I	3 (43)	4 (57)	2.19	0.061
II	6 (46)	13 (54)		
III	4 (80)	1 (20)		
IV	4 (66.7)	2 (33.3)		
V	3 (100)	0		
BDI score after treatment: (mean±SD)	11.70±8.7	1.15±0.813	t=5.4	<0.001*

I: bipolar major depression (in a major depressive episode). II: major depressive disorder. III: major depressive disorder (catatonic depression). IV: major depressive disorder (melancholic subtype). V: major depressive disorder (seasonal affective disorder). BDI, Beck depression inventory; ECT, electroconvulsive therapy.

Table 3 Comparison between ketamine and electroconvulsive therapy on their effect on Beck depression inventory score over the 13 assessment sessions

Source	*d.f.*	Mean square	*F*	Significance	Partial η^2
Time	2.398*	25308.8	182.46	0.000	0.828
Time X group	2.398*	6936.42	50.007	0.000	0.568
Error	91.131*	138.7			
Group	1	11336.89	21.966	0.000	0.366
Error	38	516.1			

*Greenhouse-Geisser correction.

Therefore, we investigate the efficacy of ketamine vs ECT in hospitalized patients with resistant MDDs.

Regarding age and sex our result shows that there is a statistically insignificant differences between the studied patients regarding sex (χ^2 = 0.752, P = 0.467) and age (χ^2 = 2.27, P = 0.051). Our results came in agreement with Zhang *et al.* [19], who reported that there was no significant differences regarding age and sex at the baseline depression scores between the two groups [19]. Our results also came in agreement with Arabzadeh *et al.* [20], who reported that baseline characteristics of participants were not significantly different between the two treatment groups, including age, sex, and disease [20]. Our results also came in agreement with Dong *et al.* [21], who reported that there was no significant difference in gender and age in all groups (P > 0.05) [21]. Also, Ghasemi *et al.* [22] found that patients' age ranged between 20 and 74 years with a mean of 37.6 years (SD: 15.05). Ten patients in both groups were women (56%). Patients received their first target treatment with an average of 12.94 (SD: 10.2) days after entering the hospital. Nine (50%) patients were randomized in the ketamine group and other nine (50%) received the ECT. Comparison of demographic features and baseline depression scores did not show a significant difference between two groups.

In this study, there was statistically insignificant differences between the studied patients regarding the types of depression (P = 0.061). Bipolar major depression and MDD were represented in 57 and 54% in the ECT group and 43 and 46% in the ketamine group, respectively. Also, catatonic depression, melancholic subtype, and seasonal affective disorder were represented by 80, 66.7, and 100% in the ketamine group vs 20, 33.3, and 0.00% in the ECT group, respectively. Our results came in agreement with Zhang *et al.* [19], who reported that there were no significant differences in depressive symptoms (types of depressive patients) [19]. Also, our results about different types of depression came in agreement with a meta-analysis of Ren *et al.* [23], who conducted 16 studies including 928 patients, and reported that there was nonsignificant difference in depressive symptoms (types of depressive patients, P = 0.14) between the two groups [23]. On the other hand, our results are in disagreement with Ionescu *et al.* [24], who found that ketamine effectively reduces symptoms of depression and is particularly effective in anxious depression. The difference between our results and their results is likely due to the fact that our study did not contain the anxious depression subtype and also may be because our sample was small and the duration of follow-up was short.

In this study, there was statistically significant difference between ketamine group and ECT regarding the efficacy of both ketamine and ECT in favor of the ketamine group as ketamine has more rapid effect in

improving depressive symptoms in MDD patients and have more rapid antidepressant effects compared with ECT. Also, we found that repeated treatments with low doses of ketamine (0.5 mg/kg, once every 48 h) as well as ECT can exert rapid antidepressant effects in patients with MDD. The antidepressant effects of ketamine remained 72 h and 1 week after the last (six) injection of ketamine as measured by BDI scale. Further analysis showed significantly fewer depressive symptoms in patients who received ketamine vs those who received ECT at the first treatment and at the second treatment 72 h post-treatment. These data suggest that the antidepressant effects of ketamine are more rapid and an effective ECT in the early stages of treatment.

Our results come in line with several studies such as of the study by Phelps [25], who found that *N*-methyl-d-aspartate receptor antagonists (e.g., ketamine) is as effective as ECT in improving depressive symptoms in MDD patients, and have more rapid antidepressant effects compared with the ECT. In addition, Nobler *et al.* [26] showed similar results and demonstrated that first dose of ketamine could significantly exert rapid antidepressant effects as measured by both big BDI scale and Hamilton depression rating scale 24 h postinfusion. This effect of ketamine has been similarly observed in another cohort involving 26 treatment-resistant MDD patients [26]. Also, the results of both Kellner *et al.* [27] and Sackeim [28] stated that ECT can generally improve depressive symptoms more rapidly than conventional antidepressants; however, the onset of ECT antidepressant action suggests that a range of 5–7 treatments (~2 weeks) are required, on average, to significantly or perhaps completely reduce symptoms severity. On the other hand, ketamine has more rapid onset of action and more effectiveness in improving depressive symptoms.

On the other hand, our result is in disagreement with Sackeim *et al.* [29], who found that there was no statistically significant difference between ketamine group and ECT group and stated that both treatments demonstrate similar response and remission rates in clinical trials. The difference between our results and their results may be due to different demographic and genetic factors [29].

Finally, due to the unavailability of the ECT apparatus equipped with electroencephalography, the investigators were unable to record seizure durations by electroencephalography. Moreover, in the current study we included a small number of patients; therefore, more studies using a higher number of participants are needed to clarify the efficacy of ketamine treatment in MDD patients. Considering the fact that intravenous administration of ketamine might have some unwanted effects on hemodynamic parameters including heart rate and blood pressure as there was an increase in systolic blood pressure as well as heart rate in three patients after the second and third dose of ketamine, which was temporary and this rise was not clinically significant. In the ECT group, hemodynamic parameters were not significantly altered [14]; some recent studies have shown that other routes of ketamine administration such as intranasal treatment [29] or oral treatment [15,16] could be well tolerated and be effective in the treatment of mood disorders. Therefore, they could be a useful and easier way for long-term ketamine administration in MDD patients.

In this study, we found that repeated treatments with low doses of ketamine (0.5 mg/kg, once every 48 h) as well as ECT can exert rapid antidepressant effects in patients with MDD. The antidepressant effects of ketamine remained 72 h and 1 week after the last (six) injection of ketamine as measured by BDI scale. Also, our results suggest that the antidepressant effects of ketamine are more rapid and an effective ECT, in the early stages of treatment. Our results come in line with several studies as the work of Phelps *et al.* [26] which showed similar results and demonstrate that the first dose of ketamine could significantly exert rapid antidepressant effects as measured by both big BDI scale and Hamilton depression rating scale 24 h postinfusion. This effect of ketamine has been similarly observed in another cohort involving 26 treatment-resistant MDD patients [30]. On the other hand, our result is in disagreement with Kellner [28] who found that there was no statistically significant difference between the ketamine group and ECT group and stated that both treatments demonstrate similar response and remission rates in clinical trials. The difference between our results and their results may be due to the different demographic and genetic factors [28].

Conclusion

The results of this study concluded that there was statistically significant difference between ketamine group and ECT regarding the efficacy of both ketamine and ECT in favor of the ketamine group as ketamine has more rapid effect in improving depressive symptoms in MDD patients and have more rapid antidepressant effects compared with ECT. More studies using a higher number of participants are needed to clarify the efficacy of ketamine treatment in MDD patients. Further analysis showed significantly fewer depressive symptoms in patients who received ketamine vs those who received ECT as the treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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