

Factors connected with efficacy of single ketamine infusion in bipolar depression

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Summary

Aim. The aim of this study was to evaluate the efficacy of single ketamine infusion and clinical and biochemical factors connected with such efficacy, in patients with bipolar depression, which had not improved on antidepressant treatment.

Methods. The study included 42 patients (32 women, 10 men), aged 22-67 years, with bipolar depression. They received ≥ 1 mood-stabilizing medications of first and/or second generation. After discontinuation of antidepressants (≥ 7 days), intravenous infusion of ketamine (0.5mg/kg body weight) was performed. The assessment of depression by the 17-item Hamilton Depression Rating Scale was made before, and after 1, 3, 7 and 14 days following administration of ketamine. The assumed criterion for clinical improvement was the reduction of $\geq 50\%$ score on the Hamilton scale after 7 days. In a subgroup of 20 patients, prior to administration of ketamine, serum concentrations of homocysteine, vitamin B12, folic acid, neurotrophins and inflammatory proteins were measured.

Results. In the whole group, the severity of depression on the Hamilton scale decreased significantly 24 hours after administration of ketamine from 22.6 ± 5.1 to 15.6 ± 7.4 points. After 7 days it was 13 ± 7 and after 14 days - 11.8 ± 7.8 points. Patients showing clinical improvement ($n=22$) had significantly higher frequency of alcohol addiction and family history of alcoholism. Biochemical tests in the subset of 20 patients demonstrated that those with clinical improvement ($n=10$) had higher serum concentrations of vitamin B12 and receptor-1 Vascular Endothelial Growth Factor before administration of ketamine. Ketamine infusion was well tolerated.

Conclusions. The results confirm a rapid antidepressant effect of ketamine infusion maintaining for 2 weeks, in a considerable proportion of patients with bipolar depression, and good clinical tolerance of such procedure. Also, some clinical and biochemical factors associated with ketamine efficacy were shown.

Key words: Ketamine, bipolar depression, antidepressant drugs

Introduction

A major problem in the treatment of depression is a delayed therapeutic effect of antidepressants (average 4-8 weeks) and increasing drug resistance. As many as

25-40% of patients do not respond satisfactory to antidepressants. It has been shown that the number of drug-resistant patients is increasing, and doctors are not able to provide fully effective treatment to approximately one third of patients with a diagnosis of depression [1].

In recent years it has been demonstrated that glutamatergic system plays an important role in the mechanism of action of antidepressant drugs [2]. Antidepressant drugs exert a significant effect on the glutamatergic NMDA (N-methyl-D-aspartate) receptors, causing a reduction in homologue NR-1 in the cerebral cortex and subcortical structures and the reduction of mRNA expression of NR2A and NR2B subunits of this receptor [3]. After administration of antidepressant drugs, an increase in AMPA glutamate receptors (alpha-amino-3-hydroxy-5-methyl-4-isoxalepropionic acid) in the hippocampus [4] and a simultaneous increase in mRNA expression of the brain-derived neurotrophic factor (BDNF) was shown [5]. Changes in glutamatergic system during treatment of depression result in a decrease of glutamatergic neurotransmission. [6]

Ketamine is a derivative of phencyclidine and acts antagonistically on NMDA receptors. It also affects the sigma 1 receptor, norepinephrine transporter (NET), opioid receptor μ and the serotonin transporter (SERT). The drug is widely used in anesthesia, for inducing a so-called "dissociated anesthesia". In 2000, Berman et al [7] demonstrated in 4 patients with depression a rapid antidepressant effect, lasting for about two weeks, after 40-minute intravenous infusion of ketamine, at a dose of 0.5 mg/kg body weight. Six years later, Zarate et al [8] performed a placebo-controlled, double-blind crossover study in a group of 17 patients with treatment-resistant depression. In 29% of these patients, a remission of symptoms, and in 71%, symptom reduction at 24 hours after infusion was observed. As many as 35% of patients maintained symptomatic improvement for 1 week after ketamine infusion. Recent studies have also shown a reduction in suicidal thoughts and intentions after ketamine administration; this effect appeared as early as after a few hours and continued until 10 days [9, 10].

In 2010, Diazgranados et al [11] reported a beneficial effects of ketamine infusion as an adjunct to mood stabilizers (lithium or valproate) in patients with bipolar depression. Clinical improvement was maintained for 14 days in 71% of patients, and the difference versus placebo was observed on the second day after the infusion. A replication of these results was obtained recently by Zarate et al [12], who, after infusion of ketamine, demonstrated an improvement in 12 of 15 patients (79%), maintained for 14 days.

In the last year, some review papers were published on the use of ketamine in depression, based on a large number of patients, exploring the effect of multiple ketamine administration, as well as research studies aimed to delineate factors connected with beneficial effect of ketamine in depression [13-16].

In our Poznan centre, research on single infusion of ketamine in patients with bipolar depression has been performed since 2011. Initial clinical experiences on a group of 25 patients have been previously reported [17]. The aim of the present study was to evaluate the effectiveness of single infusion of ketamine in a larger group (42 patients with bipolar depression receiving mood stabilizers, in which the use of antidepressant drugs failed to bring a sufficient improvement), as well as possible clinical and biological factors connected with beneficial effect of ketamine infusion.

Methods

Subjects studied

The study included 42 patients (32 women, 10 men), aged 22–67 years (mean 48 ± 11.5 years) with bipolar depressive episode. All patients were hospitalized at the Department of Adult Psychiatry, University of Medical Sciences in Poznań. The average age of illness onset in patients was 31 years (± 13), and the average length of a depressive episode was 8.4 (± 2.1) months. Prior to ketamine infusion, patients were hospitalized on average 21 days (± 5).

All patients received at least one mood-stabilizing *drug of 1st or 2nd generation* [14] (lithium carbonate – 26 patients, quetiapine – 26 patients, valproate – 9 patients, carbamazepine – 7 patients, lamotrigine – 14 patients, aripiprazole – 4 patients and topiramate – 1 patient). All patients had previously been treated with antidepressant drugs without sufficient improvement. The antidepressant used prior to infusion of ketamine was venlafaxine in 17 patients, in 11 – paroxetine, in 7 – bupropion, sertraline, in 5 – mirtazapine, in 3 – clomipramine, in 2 – reboxetine, fluvoxamine and in 1 – fluoxetine, mianserin, escitalopram, citalopram, duloxetine and amitriptyline.

Procedure of ketamine infusion

Before infusion of ketamine, Patients had an array of laboratory tests (blood count, electrolytes, urinalysis, determination of thyroid hormones), ECG and thoracic X-ray. They were consulted by cardiologist and anesthetist in order to exclude any contraindication for intravenous ketamine. All antidepressants were discontinued for at least 7 days prior to infusion. On the day of study, each patient received a 40-minute infusion of ketamine, 0.5mg/kg body weight. Infusion started at 8.00. During the infusion and for 6 hours after the administration of ketamine basic vital signs (blood pressure, heart rate, oxygen saturation) were monitored.

Psychometric assessment

Psychometric evaluation was performed by means of the 17-item Hamilton Depression Rating Scale - HDRS). The assessments were made immediately before ketamine infusion and after 6th and 12th hours, and 2, 3, 7, 10 and 14 days following this procedure. The severity of depressive symptoms prior to infusion of ketamine was at least 18 points on the HDRS (22.5 ± 5). The assumed criterion for clinical improvement was the reduction of $\geq 50\%$ on the HDRS score after 7 days, compared with baseline values. The criterion for remission was ≤ 7 points on the HDRS.

Laboratory studies

In a subgroup of 20 patients, prior to infusion of ketamine, estimations of serum concentrations of following substances were performed: homocysteine, folic acid, vitamin B12 ; neurotrophins: BDNF, nerve growth factor (NGF), neurotrophin 3

(NTF3), neurotrophin 4 (NTF4), glial-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF) and its receptors R1 and R2 and proteins associated with inflammation: C-reactive protein (CRP), intracellular adhesion molecule-1 (ICAM-1) and E-selectin.

The study was approved by the Bioethics Committee of Poznan University of Medical Sciences.

Results

Severity of depression (mean \pm SD) measured with HDRS before and after administration of ketamine is shown in Figure 1.

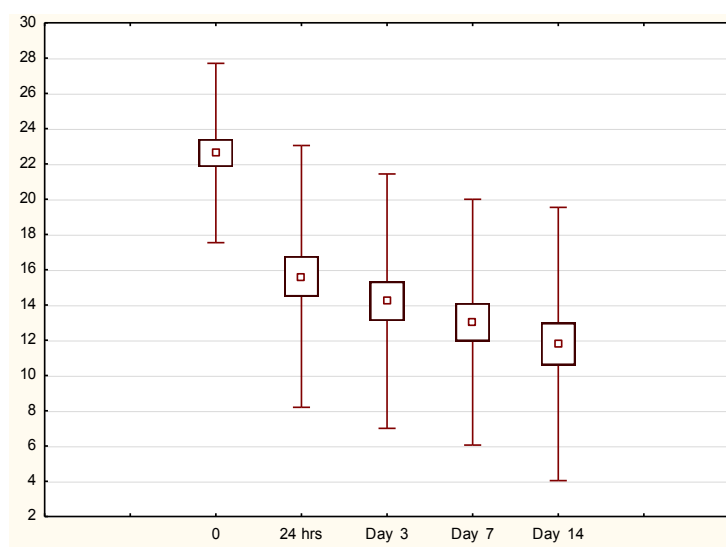


Figure 1. Severity of depression (mean \pm SD) measured with Hamilton Depression Rating Scale before and after 1, 3, 7 and 14 days following administration of ketamine in 42 patients

After intravenous administration of ketamine, statistically significant decrease of HDRS score as early as after 24 hours has been observed. Intensity of depression in patients prior to intravenous administration of the drug measured on HDRS was 22.6 ± 5 points. This decreased to 15.6 ± 7.4 points after 24 hours ($p < 0.001$, t-test for related data), to 14.2 ± 7.2 points on the 3rd day, to 13 ± 7 points on the 7th day and to 11.8 ± 7.8 points after two weeks following ketamine infusion.

On the 7th day after ketamine infusion, 22 subjects met criteria for improvement (reduction of $\geq 50\%$ on the HDRS compared with baseline), and remission was achieved in 26% of patients. After 14 days, the number of people with improvement remained the same, however, the number of patients in remission increased to 17 (40%).

In Table 1 – *next page*, clinical factors in a group of 22 persons meeting the criteria for improvement (responders) with a group of the remaining 20 patients (non-responders) are compared.

Table 1. Clinical factors in responders and non-responders to single ketamine infusion

	All patients N = 42	Responders N = 22	Non-responders N = 20
Gender (F/M)	32/10	16/6	16/4
Age	48 ± 11 y	49 ± 10 y	46 ± 13 y
Age of illness onset	31 ± 13 y	32 ± 13 y	30 ± 14 y
Alcohol abuse/ dependence	13	10*	3
Family history of psychiatric illness	30	16	14
Family history of alcoholism	17	13**	4
Duration of depressive episode (weeks)	20.4 ± 8.3	18 ± 8.4	23 ± 7.5

* difference significant, $p=0,033$ (chi² test)

** difference significant, $p=0,023$ (chi² test)

In the whole group, 13 patients abused or were dependent on alcohol. Among them ten (45%) belonged to responders and 3 (15%) to non-responders which makes a statistically significant difference ($p = 0.033$, chi² test). Also the percentage of patients with family history of alcoholism was significantly higher in ketamine responders than in non-responders (59 vs 20%, respectively, $p = 0.023$, chi² test). Other clinical factors did not differ in both groups.

In Table 2, results of biochemical tests performed prior to administration of ketamine in a group of 20 patients, including 10 responders and 10 nonresponders are compared.

Table 2. Results of biochemical tests performed prior to administration of ketamine in a group of 20 patients, including 10 responders and 10 nonresponders

	All patients n=20	Responders n=10	Non-responders n=10
homocysteine (µM/L)	14.1 ± 6.3	14.5 ± 6.4	14.1 ± 6.7
CRP (µg/mL)	1.6 ± 2.2	1.3 ± 2.2	1.9 ± 2.3
ICAM (ng/mL)	204 ± 122	171 ± 96	237 ± 142
E-selectin (ng/mL)	19.6 ± 12	21 ± 14	18 ± 10
VEGF (pg/mL)	165 ± 111	147 ± 95	183 ± 127
R1-VEGF (ng/mL)	13.5 ± 5.4	26 ± 7.6**	8.6 ± 2.2
R2-VEGF (ng/mL)	11 ± 3.5	11 ± 2.8	11 ± 4.2
Vitamin B12 (pg/mL)	330 ± 150	402 ± 167*	274 ± 90
Folic acid (ng/mL)	6.0 ± 2.4	5.1 ± 2.0	6.4 ± 2.5
BDNF (µg/mL)	40.7 ± 7.1	40.3 ± 7.2	41.0 ± 7.5

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NGF (ng/mL)	10.6 ± 19.7	13.9 ± 1.7	7.4 ± 13.7
NT3 (ng/mL)	155 ± 419	274.9 ± 643.5	34.9 ± 48.2
NT4 (ng/mL)	38.6 ± 119	71.4 ± 166.4	5.7 ± 4.3
GDNF (ng/mL)	35.5 ± 89.3	52.2 ± 114.8	11.6 ± 18.9

* difference significant, $p = 0,047$, t-test

** difference significant, $p = 0,030$, t-test

CRP – C-reactive protein, ICAM – intracellular adhesion molecule-1, VEGF-vascular endothelial growth factor, R1-VEGF Receptor 1, R2-VEGF Receptor 2, BDNF – brain-derived neurotrophic factor, NGF – nerve growth factor, NT3 – neurotrophin 3, NT4 – neurotrophin 4, GDNF – glial-derived neurotrophic factor

Patients responding well to ketamine infusion had significantly higher levels of serum vitamin B12 (402 vs 274 pm/ml, $p=0.047$, t-test) and higher concentrations of receptor 1 for vascular endothelial growth factor (VEGF) ($p = 0.030$, t-test) compared to non-responders. The values of other biochemical tests made prior to ketamine infusion did not differ between responders and nonresponders. Concentrations of certain neurotrophins were higher in the group of responders, however, the difference versus non-responders did not reach statistical significance due to great variation of results.

In Table 3 clinical parameters in a group of 20 patients, who had biochemical studies, with a group of 22 patients, who had not such studies, were compared.

Table 3. Comparison of clinical parameters in a group of 20 patients who had biochemical studies with a group of 22 patients who had not such studies

Clinical data	Biochemical studies N = 20	No biochemical studies N = 22
Gender F/M	18/2	14/8 *
Age	50 ± 11 y	46 ± 12.1 y
Age of illness onset	34 ± 13 y	29 ± 13 y
Duration of depressive episode (months)	6 ± 2 m	6 ± 2 m
Alcohol abuse/ dependence F/M	3/1	6/3
Family history of psychiatric illness	12/2	11/5
Responders to ketamine	10/20	12/22

* difference significant $p=0,045$ (chi² test)

The group without biochemical tests contained more men (36%) compared with the group in which the tests was performed (10%) ($p = 0.045$, chi² test) and showed an earlier onset of the illness, but this difference was not statistically significant.

The infusion of ketamine was well tolerated and no serious side effects have been recorded. In the majority of patients during the infusion a slight increase in blood pressure was observed as well as transient symptoms of depersonalization and derealization, reaching in one patient a level of psychotic experience, which resolved after completion of the infusion.

Discussion

The results indicate a beneficial antidepressant effect of a single infusion of ketamine in patients with bipolar depression receiving mood stabilizers, in which treatment with antidepressants did not bring a satisfactory effect. This confirms the results of American researchers [11, 12], indicating a rapid antidepressant effect of single ketamine infusion in a similar group of patients. Similarly to the above mentioned research, significant effect of the infusion was evident on the next day after infusion. The percentage of patients with improvement in our study was somewhat lower than that of American researchers (52% vs 71% and 79%), however, it is remarkable that 40% of patients in our study met remission criteria at two weeks after infusion (≤ 7 points on a scale HDRS). The percentage of patients who met criteria for improvement after 7 days was similar to that obtained in Murrugh et al [15] paper, which was 45%. They included patients with treatment-resistant unipolar depression not receiving antidepressants and mood stabilizers, and the criterion of improvement was the reduction of the depression severity by $\geq 50\%$ compared with baseline values in MADRS (Montgomery-Asberg Depression Rating Scale).

The percentages of improvement and remission achieved in our study in bipolar depression after ketamine infusion significantly exceeded the results obtained by classical antidepressant treatment. Compared with American reports [11,12], our study included a larger group of patients with bipolar disorder, but we employed an open trial. Another difference in relation to American studies was using by our patients mood stabilizers of both the first and second generation.

In this study, intravenous ketamine was relatively well tolerated by patients. Side effects, such as depersonalization and derealization were only recorded during the infusion and were not severe. Similar observations were made by other researchers [12, 19].

We observed a better effect of ketamine in patients who abused or were dependent on alcohol and in patients with family history of alcoholism. This may correspond to the results obtained by Luckenbaugh et al [20] who, among 33 patients received intravenous ketamine a better therapeutic in patients with family history of alcoholism. It may be speculated that alcohol effect on glutamatergic NMDA receptors may play in the mechanism of this phenomenon [21].

Among biochemical factors associated with a favourable effect of ketamine we found higher baseline levels of vitamin B12 (cyanocobalamin). This corresponds with other studies indicating that higher levels of this vitamin are connected with better efficacy of antidepressant drugs [22, 23]. Perhaps, the low levels of vitamin B12 were related to previous poor efficacy of antidepressant drugs in some of our patients. Concentration of vitamin B12, negatively correlates with the level of amino acid homocysteine, an agonist of NMDA receptors, which could play a role in the pathogenesis of depression [24, 25].

In 2011, Autry et al.[26] showed in experimental study that blocking NMDA receptor by ketamine results in an increase of BDNF activity, which may play a significant role in the mechanism of antidepressant effect of ketamine. Machado - Vieira et al.

[27] showed no changes in serum BDNF levels at 6 hours after ketamine infusion. In this study there was no difference in baseline serum concentration of BDNF and other neurotrophic factors between responders and non-responders to ketamine infusion. However, in our previous study, we found a significant decrease in BDNF levels after 7 days in non-responders [28]. In recent American study, a significant correlation between serum BDNF levels, and the intensity of depression both after 4 hours and 3 days after administration of ketamine was found [29]. These results may indicate that the activity of BDNF system in depressive patients can be associated with the mechanism of antidepressant action of ketamine.

In this study we have shown a higher concentration of receptor 1 (VEGF) in patients with a better effect of ketamine. Recent studies point to a role of VEGF in the pathogenesis of depression and antidepressant action [30]. The researchers in Łódź also found a connection between a predisposition to depression and a polymorphism of receptor 2 VEGF gene, which receptor occurs primarily in central nervous system [31]. The results obtained in this study can also indicate a possibility of receptor-1 VEGF in the mechanism of ketamine efficacy.

In summary, the results of this study confirm a rapid antidepressant effect of ketamine infusion maintained for at least two weeks, in a considerable percentage of patients with bipolar depression receiving mood stabilizers, resistant to previous antidepressant treatment. They also point on some factors which can be connected with beneficial effect of ketamine, such as alcohol abuse/dependence as well as higher levels of vitamin B12 and receptor-1 VEGF before ketamine infusion.

Факторы эффективности одноразового вливания кетамина при депрессии во время течения двухполюсной аффективной болезни

Содержание

Задание. Оценка эффективности одноразового вливания кетамина и клинических, а также биохимических обуславливающих его эффект у пациентов с депрессией во время течения двухполюсной аффективной болезни (АДБ), у которых применение антидепрессивных препаратов не приносит терапевтического эффекта.

Метод. Исследовано 42 пациентов (32 женщины и 10 мужчин) в возрасте 22–67 лет с депрессией во время двухполюсной аффективной болезни (АДБ) получающих ≥ 1 лекарство нормотивного действия первой или второй генерации. После изъятия противодепрессивных препаратов (≥ 7 дней) вливался кетамин (0,5 мг/кг массы тела). Оценка депрессии по 17-пунктовой шкале депрессии Гамильтона проведена перед и после 1, 3, 7 и 14 дней введения кетамина. Критерием клинического улучшения уменьшение на $\geq 50\%$ пунктации в шкале Гамильтона после 7 дней. В подгруппе 20 пациентов перед введением кетамина проведено исследование концентрации гомоцистеина, витамина B12, фолиевой кислоты нейротрофина и белков воспалительной реакции.

Результаты. Во всей группе больных утяжеление депрессии в шкале Гамильтона значительно уменьшилось после 24 часов со времени введения кетамина с 22 ± 51 до $15,6 \pm 74$ пункта. После 7 дней равнялось 13 ± 7 пунктов и после 14 дней с $11,8 \pm 78$ пункта. У больных с клиническим улучшением (22) существенно чаще появлялась зависимость от алкоголя и алкоголизм в семье. Биохимические исследования в подгруппе 20 пациентов показали у лиц с клиническим улучшением (10 больных) высшие концентрации витамина B12 и рецептора 1 фактора роста сосудистого эндотелия в сыворотке перед введением кетамина. Вливание кетамина хорошо переносилось больными.

Выводы. Полученные данные подтверждают быстрый антидепрессивный эффект инфузии кетамина удерживающийся в течение 2 недель, у значительного числа больных с депрессией при АДБ, а также хорошую клиническую толерантность такого вмешательства. Показаны также некоторые клинические факторы такой процедуры, а кроме того и биохимические показатели, связанные с положительным влиянием кетамина.

Ключевые слова: противодепрессивные лекарства, кетамин, депрессия во время двухполюсной аффективной болезни

Faktoren der Effektivität von einmaliger Ketamin – Infusion in Depression im Verlauf der affektiven bipolaren Störung

Zusammenfassung

Ziel. Das Ziel der Arbeit war die Bewertung der Effektivität einer einmaligen Infusion mit Ketamin und der klinischen und biochemischen Faktoren, die sie bei den Patienten mit der Depression im Verlauf der affektiven bipolaren Störung bedingen, und bei denen die Einnahme von Antidepressiva keine Verbesserung gebracht hatte.

Methode. Es wurden 42 Patienten (32 Frauen und 10 Männer) im Alter von 22 bis 67 Jahren mit Depression im Verlauf der affektiven bipolaren Störung untersucht. Sie bekamen ≥ 1 normothymisches Mittel der ersten oder/und zweiten Generation. Nach dem Entzug von Antidepressiva (\geq) Tage wurde die Infusion mit Ketamin (0,5 mg/kg Körpermasse) durchgeführt. Die Depression in der 17-Items-Skala der Depression von Hamilton wurde vor der Gabe von Ketamin und nach dem 1., 3., 7., und 14. Tag bewertet. Die Senkung der Items um 50% in der Hamilton-Skala nach 7 Tagen wurde zum Kriterium einer klinischen Besserung. In der Untergruppe von 20 Patienten wurde vor der Ketamin – Infusion die Untersuchung auf Konzentration von Homozystin, Vitamin B12, Folsäure, Neurotrophinen und Proteine durchgeführt.

Ergebnisse. In der ganzen Gruppe verringerte sich signifikant die Intensität der Depression nach 24 Stunden von der Gabe von Ketamin. Sie sank von $22,6 \pm 5,1$ auf $15,6 \pm 7,4$ Items. Nach 7 Tagen betrug sie 13 ± 7 Items und nach 14 Tagen $11,8 \pm 7,8$ Items. Bei den Personen mit der klinischen Besserung ($n=22$) trat signifikant häufiger die Alkoholabhängigkeit und Alkoholkrankheit in der Familie auf. Die biochemische Untersuchung erwies in der Untergruppe der 20 Patienten eine höhere Konzentration von Ketamin bei den Personen mit der klinischen Besserung ($n=10$), höhere Konzentration von B12 Vitamine und Rezeptors 1 des Vascular Endothelial Growth Factor im Blutserum vor der Gabe von Ketamin. Die Infusion mit Ketamin war gut verträglich.

Schlussfolgerungen. Die Ergebnisse bestätigen den schnellen antidepressiven Effekt der Infusion mit Ketamin, der sich 2 Wochen lang bei einem größeren Teil der Patienten mit der Depression im Verlauf der affektiven bipolaren Störung hält und ein gutes Ansprechen dieses Verfahrens. Es wurde auch auf manche klinischen und biochemischen Faktoren hingewiesen, die mit der positiven Wirkung von Ketamin verbunden sind.

Schlüsselwörter: Antidepressiva, Ketamin, Depression im Verlauf der affektiven bipolaren Störung

Les facteurs liés avec l'efficacité de l'infusion unique de kétamine dans la dépression au cours du trouble bipolaire

Résumé

Objectif. Evaluer l'efficacité de l'infusion unique de kétamine et de facteurs cliniques et biochimiques liés avec elle chez les patients avec le trouble bipolaire résistant à la thérapie antidépressive.

Méthode. On examine 42 patients (32 femmes, 10 hommes), âgés de 22–67 ans, souffrant de la dépression au cours du trouble bipolaire, traités de ≥ 1 médicament antidépresseur de première ou deuxième génération. Une semaine (≥ 7 jours) après la fin de ce traitement on applique unique infusion de kétamine (0,5 mg/kg poids du corps). L'analyse de la dépression est faite après 1, 3, 7,

14 jours après cette infusion – en usant the Hamilton Depression Rating Scale – échelle de 17 points. La diminution de $\geq 50\%$ de points de l'échelle d'Hamilton est traitée comme critère d'amélioration après 7 jours. Avant la thérapie de kétamine dans le groupe de 20 patients on a examiné encore la concentration d'homocystéine, de vitamine B12, d'acide folique, des neurotrophines et des protéines inflammatoires dans le sérum.

Résultats. Dans le groupe entier la sévérité de la dépression diminue fortement après 24 heures après l'infusion de kétamine : de $22,6 \pm 5,1$ points. Après 7 jours : 13 ± 7 , après 14 jours : $11,8 \pm 7,8$ points. Les patients avec l'amélioration clinique ($n=22$) plus souvent sont alcooliques et ils ont les alcooliques dans leurs familles. Les testes biochimiques des 20 patients examinés démontrent chez les patients avec l'amélioration ($n=10$) la plus grande concentration de vitamine B12, et du récepteur-1 de Vascular Endothelial Growth Factor dans le sérum avant la thérapie de kétamine. Cette thérapie est bien tolérée.

Conclusions. Ces résultats attestent l'effet antidépresseur rapide de l'infusion unique de kétamine qui dure presque deux semaines chez la plupart de patients avec la dépression dans le cours du trouble bipolaire. Cette thérapie est aussi bien tolérée. On décrit aussi certains facteurs cliniques et biochimiques liés avec cette efficacité de kétamine.

Mots clés : kétamine, dépression au cours du trouble bipolaire, médicaments antidépresseurs

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