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Ketamine Infusion (KI) in Treatment Resistant Depression (TRD): Retrospective Clinical Data Analysis

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Abstract

Objective: The aim of this paper is to present the clinical data analysis results from a service delivering ketamine infusion, repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy for people with treatment resistant depression (TRD). **Methods:** The study was a retrospective investigation of routinely collected data on patients receiving ketamine infusion between 2017 and 2019. Measures used were the clinician-rated Clinical Global Impression (CGI) and self-reported Beck Depression Inventory (BDI) and Quick Inventory of Depressive Symptomatology (QIDS-SR). The outcome data of 28 patients with TRD were analysed. A minimum course of treatment was defined as three ketamine infusions. **Results:** Response combined with partial response, response, and remission rates respectively were 42.3%, 23.1% and 4.2% for the BDI; 18.2%, 9.1% and 0% for the QIDS-SR; 50%, 18.2% and 4.6% for the CGI. There was a statistically significant improvement on the BDI with a medium effect size (0.63). There was not a significant improvement in the CGI or QIDS-SR. **Conclusions:** The results show a mixed picture the impact ketamine on symptoms of depression in TRD over the course of multiple infusions. The results need to be viewed in the context of clinical outcome data collection: outcome scores are taken prior to treatment and so are at a point when ketamine is not having an active effect. The findings can inform the availability of ketamine infusion as a treatment option for TRD where treatment adhering to national guidelines has not succeeded. A qualitative investigation of the experience of people receiving ketamine would provide further insights.

Keywords

Ketamine Infusion, Repetitive Transcranial Magnetic Stimulation (rTMS),

1. Introduction

Treatment resistant depression (TRD) does not have a single universally accepted definition (Berlim & Turecki, 2007). Many people experiencing major depressive disorder (MDD) do not respond to psychopharmacological or psychotherapy treatments and some, who respond initially, may relapse and become unresponsive to subsequent treatment. Over half of people may not experience remission after the first or second antidepressant treatment course, and one-third may not experience remission after four different antidepressant treatment courses (Rush et al., 2006; Souery et al. 2007). Non-response rate to psychotherapy (typically cognitive behavioural therapy), has been reported at 70% (Griffiths & Griffiths, 2014).

Depression is the leading cause of ill health and disability worldwide (WHO, 2017). Between 12% - 20% of depressed patients have TRD, and having TRD results in greater loss of economic contribution (Eaton et al., 2008; Nemeroff, 2007). Around 75% of the total costs related to depression are attributable to treatment resistant depression (TRD) (Mrazek et al., 2014).

In 2008 the US Food and Drug Administration (FDA) approved repetitive Transcranial Magnetic Stimulation (rTMS) for depression treatment (Janicak & Dokucu, 2015). The UK's National Institute for Health and Care Excellence (NICE) (IPG 542, 2015) stated that it is safe and effective in reducing depressive symptoms compared to sham TMS, and it does not require hospital admission or anaesthesia (NICE, 2015). TMS neuromodulation employs an electromagnetic coil placed against the scalp to deliver a short, powerful magnetic field pulse to induce electric currents in the cerebral cortex (Hardy et al., 2016). Evidence indicates that rTMS changes brain activity, metabolism and connectivity that relate to emotional processing (Kito, Fujita, & Koga, 2008); however, the exact mechanism of action is unknown (Hardy et al., 2016). rTMS is effective in treating the symptoms of depression (Griffiths et al., 2019; Health Quality Ontario, 2016).

Studies continue to prove the efficacy of ECT for treating severe depression (Mohn & Rund, 2016; The UK ECT Review Group, 2003), with many showing ECT to be superior to pharmacotherapy (The UK ECT Review Group, 2003). ECT is still the most effective treatment for severe depression (Mohn & Rund, 2016). ECT is associated with improvement in quality of life as assessed by both physicians and patients (Antunes & Fleck, 2009).

Ketamine is an N-methyl-D-aspartate receptor antagonist (Andrade, 2018). Aligned with the glutamatergic hypothesis of depression (Sanacora et al., 2012), ketamine has been proposed as a treatment for depression (Hashimoto, 2009; Pittenger & Duman, 2008; Tardito et al., 2006). When used to treat severe de-

pression, evidence indicates that a subanaesthetic ketamine treatment dose provides a rapid and effective, but short term, antidepressant action (Kishimoto et al., 2016; Xu et al., 2015), might decrease suicidal ideation (Canuso et al., 2018) and cause a short term reduction in suicidality (Xu et al., 2015).

Ketamine achieves its maximum effect in 24 hours after administration and last up to seven days. Adverse effects include psychotic and dissociative effects, blood pressure and heart rate fluctuations, blurred vision and drowsiness (Grady et al., 2017). A meta-analysis concluded that ketamine has a rapid onset (within 1 day) antidepressant efficacy for those who have not benefitted from antidepressants, used as monotherapy or in combination with oral antidepressants (Fond et al., 2014). Another meta-analysis found ketamine exerts a large antidepressant effect in patients with MDD and bipolar disorder at 4 hours, 24 hours and 7 days (Coyle & Laws, 2015). A review revealed seven RCTs of ketamine in MDD and bipolar disorder and it concluded that it has shown promise in quickly reducing depression symptoms in TRD (Grady et al., 2017). Ketamine dependence and withdrawal symptoms have been reported (Morgan et al., 2012).

In the US the FDA recently approved a ketamine nasal spray (Spravato-Esketamine [Canuso et al., 2018]) medication for treatment-resistant depression (FDA, 2019); and it is now available to treat depression in the USA. However, a nasal spray cannot deliver as precise a dose as an IV infusion (Gould et al., 2019). The UK's Royal College of Psychiatrists (2017) considers ketamine for depression a "novel treatment". A review and analysis of the ethical considerations in off-label ketamine use for treatment-resistant depression concluded it does not violate ethical principles, that guidelines for good practice should be enacted, and that the risk potential be monitored (Singh et al., 2017). In the UK intravenous ketamine is offered by two NHS healthcare providers to patients to treat depression as an "off-label" treatment.

Low doses of ketamine can increase motor cortex excitability to transcranial magnetic stimulation (Lazzaro et al., 2003). Very limited evidence has been reported on the combination of intravenous ketamine infusion and TMS treatments for depression. In one study subjects with major depressive disorder were pre-treated with ketamine or placebo prior to administration of theta burst stimulation (TBS). The study concluded that future research should examine the potential clinical impact of combining these treatments (Leuchter et al., 2017). A single case study of combined TMS/ketamine treatment for 12 weeks in TRD reported a significant reduction in depression but not remission (Best, 2015). Another single case study of TMS/ketamine combination therapy in TRD reported patient depression remission, which was sustained at the two-year point (Best & Pavel, 2017). Best (2015, p. 3) stated: "We believe that modulation of the known dysfunctional cortico-thalamo-cortical circuit via the entraining effect of electromagnetic stimulation rendered the patient more responsive to the ketamine infusion. This resulted in more efficacious relief from the refractory depression... The result appears to be enduring, as the patient has been free of suf-

fering for two years”.

This paper reports analysis of routinely collected service data of patients who underwent intravenous ketamine infusion or both intravenous ketamine infusion and rTMS/ECT for TRD.

2. Methods

2.1. Design

The study was a retrospective investigation of routinely collected data on patients receiving ketamine infusions for depression between 2015 and 2019 at a UK based service provider. Demographic information (gender, age at admission), diagnosis, treatment funder, and outcomes data were extracted from clinical records containing routinely collected data. In this study, an anonymised database was created for analysis; an identity code was assigned to each patient in order to protect confidentiality so that no patient identifiers such as names, dates of birth or NHS numbers would appear on the database. The Head of Innovation and Research at Northamptonshire Healthcare NHS Foundation Trust responsible for research governance reviewed and approved the work.

2.2. Measures

The Beck Depression Inventory (BDI) is one of the most widely used self-reported measures of depression severity (Beck & Alford, 2009). The scale has high content validity, construct validity, concurrent validities, content validity, internal consistency, and reliability (Jackson-Koku, 2016). The Clinical Global Impression (CGI) rating scale is one of the most widely used assessment instruments in psychiatry (Guy, 1976). The CGI is a brief clinician-rated instrument of illness severity. There is a lack of strong evidence for the validity and therefore it is recommended as part package of assessments (Forkmann et al., 2011). The 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR) is a self-reported measure of depressive symptom severity, developed from the 30-item Inventory of Depressive Symptomatology (APA, 2000). The scale has high internal consistency and concurrent validity (Rush et al., 2006).

2.3. Process to Treatment

Patients with depressive symptoms are referred to the service by their GP or psychiatrist. A medical and physical history is taken, and patients are then assessed for a diagnosis of TRD by a psychiatrist working in the neuromodulation unit. TRD is defined as non-response to 2 or more appropriate courses of anti-depressants and a course of psychological therapy. Initial treatment of three ketamine infusions over a two to three week period to gauge the patient's response is undertaken; if patients respond further treatments are provided. rTMS protocol and length of treatment are set by the psychiatrist. Patients who lack capacity to consent to treatment are excluded. Patients are provided with information about the treatment (procedures, risks, side effects, remission/response

rates) and are required to sign a “consent to treatment” form before treatment commences; they can withdraw consent at any point. rTMS equipment suppliers are Magstim and MagVenture.

2.4. Intravenous Ketamine Infusion

An anaesthetist inserts a needle into a vein on the back of patient’s hand and sets up a syringe pump so that a dose of Ketamine is gradually infused over 40 minutes. Patients receive initial doses of 0.5 mg/kg this can be increased to 1 mg/kg depending on clinical response. The protocol is IV ketamine over 40 minutes for 3 test infusions to determine ketamine response, in those patients who do not exhibit a response after 3 ketamine infusions we discontinue ketamine and define the patient as a ketamine non-responder. In those patients who respond during the 3 test infusions will be told to return when symptoms come back or in 4 weeks whichever is the sooner.

2.5. rTMS Treatment

The site of stimulation is determined using the min-R “10 - 20” method with stimulation at the F3 electrode (Tsuzuki et al., 2016). The majority of patients received of FDA (Food and Drug Administration, 2019) depression protocol high-frequency stimulation to left dorsolateral prefrontal cortex and low-frequency inhibitory treatment to the right dorsolateral prefrontal cortex.

2.6. ECT

ECT delivery follows the NHFT (2019) protocol, which draws upon existing protocols. The Thymatron System IV ECT machine is used. A dosing algorithm based on seizure threshold (adapted from Fergusson et al. 2004) is used to determine the treating dose.

2.7. Analysis

Analysis was chosen with input from statistican. Analysis of change from baseline to the latest course treatment scores was carried out using data from 28 patients. Not all patients had data sets for all measures and so numbers per measure vary. For categorical responses with the DBI, we defined responses as a 50% or greater drop on the last assessment of treatment (Reeves et al., 2012), and 25% - 49% drop as a partial response. Remission was defined as BDI score of ≤ 12 , CGI scores of ≤ 2 (Riedal et al., 2010), and QIDS scores of < 5 (Gramer et al., 2015).

As continuous variables were not normally distributed, Wilcoxon signed-rank tests (Z) were used to compare baseline with post-treatment measures, together with the calculated effect sizes. Using non-parametric analysis (Spearman correlation coefficient), the relationship between the depression scales and ketamine treatment were explored. All tests were 2-sided, at 1% level of statistical significance. Data were analysed using statistics software package SPSS.

3. Results

3.1. Patient Characteristics

The data were collected on a sample of 28 patients with TRD, who were treated between June 2015 and July 2019. The participants' age ranged from 22 to 78 years, with a mean of 49.41 ($SD = 15.207$). Women comprised 68% of the sample; however, crosstabulation indicated they were not overrepresented, $\chi^2 (df = 1, n = 28) = 3.571, p = 0.059$.

3.2. Ketamine Treatment Outcome

Baseline depression scores were in the severe range (see **Table 1**). There was a statistically significant improvement on BDI measures after the ketamine treatment, with a medium effect size. There was not a significant improvement in CGI or QIDS-SR.

3.3. Categorical Response and Remission Rates

BDI scores showed 23.1% responded to ketamine treatment, with a further 19.2% reaching a partial response. 57.7% of patients reported no response, with 4.17% reaching remission. CGI scores showed 18.18% responded to ketamine treatment, with a further 31.82% reaching a partial response. 50% of patients reported no response, with 4.55% reaching remission. QIDS scores showed 9.10% responded to ketamine treatment, with a further 9.10% reaching a partial response. 81.82% of patients reported no response, no one reached remission.

3.4. Clinician Assessed (CGI) and Self-Reported Measures (BDI/QIDS) of Depression

There were no correlations found between the pre-treatment measures of depression, but there was a strong positive correlation between the two self-reported measures (CGI and BDI) at the last recorded day of ketamine treatment, $r = 0.71, p < 0.001$.

3.5. Impact of Other Variables

There were no differences between BDI responders and non-responders in

Table 1. Mean (SD) pre- and post-treatment scores, mean change in scores and associated Wilcoxon Signed Ranks significance tests for patients treated with ketamine.

Rating Scale	<i>N</i>	Mean \pm SD [Range]	<i>Z</i>	<i>p</i>	<i>r</i>
CGI					
Pre	24	4.67 \pm 1.31 [3 - 7]	-1.340	0.180	0.27
Post	25	4.12 \pm 1.13 [2 - 7]			
BDI					
Pre	26	41.77 \pm 10.57 [15 - 59]	-3.217	<0.001	0.63
Post	26	32.04 \pm 13.67 [1 - 52]			
QIDS-SR					
Pre	19	33.47 \pm 5.27 [23 - 41]	-0.119	0.905	0.03
Post	20	31.95 \pm 7.53 [13 - 44]			

gender ($\chi^2 = 163.0$, $p = 0.529$), age ($U = 55.5$, $p = 0.926$) and the number of treatment sessions they received ($U = 58.0$, $p = 0.929$). Similarly, no primary outcomes (age, gender, number of treatment sessions) were found to be statistically significant predictors of treatment effectiveness using binary logistic regression.

Apart from receiving ketamine treatment, some patients also received additional treatment (ECT or rTMS). Post-hoc ANOVA analysis (see **Table 2**) showed that for BDI, those with simultaneous ECT therapy scored the lowest scores, followed by those who received rTMS, and the highest depression scores were observed in those who only received ketamine treatment, suggesting ketamine works better when coupled with another form of therapy. Due to a lack of representative numbers, the gender differences between those who received rTMS at the same time as ketamine could not be calculated.

4. Discussion

The results show that a course of ketamine infusions (defined as a minimum of three) significantly improved depression on the DBI but not on the CGI or QIDS-SR. Response combined with partial response was above 42% on BDI and CGI and above 18% on the QIDS-SR; but remission rates for depression were less than 5% for all measures. The results, therefore, show a mixed picture of evidence of the impact ketamine on symptoms of depression in TRD over the course of multi infusions in clinical practice. The results need to be viewed in the context of clinical outcome data collection: outcome scores are taken prior to treatment and so are at a point when ketamine is not having an active effect.

The results may link to evidence indicating that a subanaesthetic ketamine treatment dose provides a rapid and effective, but short term, antidepressant action (Coyle & Laws, 2015; Fond et al., 2014; Grady et al., 2017; Kishimoto et al., 2016; Xu et al., 2015). For those in this dataset who experienced remission or response, this may be due to short term relief allowing them to engage in activities (social, meaningful, physical, healthy lifestyle activities) that enabled a degree of mental health recovery. A qualitative investigation, interviewing patients who have undergone clinical ketamine treatment for depression would enable an understanding of how ketamine impacted on their lives and therefore provide a detailed insight into the nature of the effects of ketamine. It would allow an

Table 2. Multiple comparisons of BDI scores of patients who received ketamine only treatment or in conjunction with either ECT or rTMS.

Dependent Variable	Additional Treatment	Additional Treatment	Mean Difference	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
BDI	None	ECT	16.44*	3.438	<0.001	8.19	24.69
	None	rTMS	5.35*	1.102	<0.001	2.71	8.00
	rTMS	ECT	11.09*	3.488	0.005	2.72	19.46

*The mean difference is significant at the 0.05 level.

understanding of the experience of the psychoactive ketamine effect and the subjective changes in mood, motivation and behaviour that resulted over time. It may also allow an investigation of any dependence and withdrawal symptoms.

There is likely to be an increase in availability and use of ketamine in the US following the FDA's recent approval of ketamine nasal spray (Spravato-esketamine) medication for treatment-resistant depression (FDA, 2019). In the UK it remains a "novel" treatment (Royal College of Psychiatrists, 2017) and it is uncertain if availability will expand beyond the two NHS healthcare providers treating depression with ketamine as an "off-label" treatment; or whether availability via private clinics will increase. Ketamine is a potential option to treat individuals with complex TRD when no further evidence-based therapies are available; nonetheless, more evidence on long-term efficacy and safety is required before inclusion in treatment algorithms of clinical practice guidelines (López-Díaz et al., 2019).

4.1. Limitations

Data were extracted from a clinical database and patient notes with some missing assessments, evidenced by the different number of subjects available for analysis on each outcome measure. Treatment was open label and adjunct to any existing antidepressant treatments, with the absence of a control. Data were from a single site in the UK limiting generalizability, however; patients were from across the UK, partially negating this. Ketamine effect trails off within 7 days.

4.2. Conclusion

More evidence is required about the longer term effects of ketamine for TRD. There is a need to effectively track the depression of people receiving ketamine at regular daily intervals following infusion; a smart phone based software application could enable this. A qualitative investigation of the experience of people receiving clinical ketamine for depression could provide insights into its effects and valuable information in relation to treatment decisions.

Conflicts of Interest

Professor Alex O'Neill-Kerr is a consultant to Magstim. No other authors have any conflicts of interest to declare.

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