ABSTRACT

OBJECTIVE
To evaluate the response of treatment resistant depression to Intravenous ketamine therapy protocol and explore the perspectives of patients regarding the acceptability of this treatment modality.

STUDY DESIGN
Mixed methods assessment, including quasi-experimental design and qualitative interviews.

PLACE AND DURATION OF STUDY
The study was conducted at the Department of Psychiatry, of a Fauji Foundation Hospital in Rawalpindi from January to June 2022.

SUBJECTS AND METHODS
Through purposive sampling, 14 patients of treatment resistant depression were used the study sample. Hamilton Rating scale for Depression (HAM-D) was used to measure response to 6 Ketamine infusions administered over 2 weeks. Paired t-test was applied to analyse changes in HAM-D scores compared to a pretreatment baseline at 1 hour, 2 weeks and 1 month after the last dose of ketamine using SPSS 26.0. Semi-structured interviews were conducted to explore the attitudes of patients regarding ketamine treatment. A Thematic analysis was performed and data driven themes were identified.

RESULTS
There was a statistically significant improvement in severity of depression scores at 1 hour and 2 weeks after the last dose of ketamine. This effect was not significantly sustained at 1 month after the last dose. Some patients expressed initial hesitation related to safety of this treatment, citing comparisons with General anaesthesia. By the end of treatment, most patients were keen to be advocates for the access to Ketamine therapy due to experiencing rapid transformational effects on severe depressive symptoms.

CONCLUSION
IV Ketamine therapy was found to be a rapid, effective and acceptable tool for treatment resistant depression; however, its long term effects could not be established.

KEYWORDS
Anti-depressive agent, Depression, HAM-D Scale, Ketamine, Treatment resistant depressive disorder.

INTRODUCTION
Depression is one of the most common mental health disorders, with a wide range of biological, psychosocial, and economic consequences. Populations in low- and middle-income countries are more vulnerable to the devastating effect of this disease, owing to limited access to effective evidence-based care. Standard treatment of depression with antidepressants may not provide complete remission in a wide range of patients. If residual symptoms, including cognitive impairment and social dysfunction, are persistent, they can cause significant distress and decline in daily functioning.

There has been considerable debate regarding the definition of treatment resistant depression (TRD); the consensus is that it is the presence of significant depressive features persisting after standard therapeutic trial of 2 antidepressants. This umbrella term serves as a clinical correlate for cases with incomplete remission, residual symptoms and poor functioning despite adequate treatment. This vulnerable group of patients requires focused treatment approaches, including traditional as well as novel interventions, keeping in mind their effectiveness and safety. Review articles on the subject have outlined several effective treatment options for TRD to ensure sustained response or continued remission. Besides standard combinations and augmentations of antidepressants, IV ketamine therapy has been recently investigated as a novel treatment option in resistant depression. Unlike conventional antidepressants that require several weeks to take effect, ketamine has shown to induce a rapid positive clinical response within hours of administration in various patients with inadequate response to standard phamaco-therapies and other forms of treatment. Most results provide support for ketamine in the rapid reduction in severity of depressive symptoms and suicidal ideation in cases of resistant depression.

As a country with limited healthcare resources, mental health services in Pakistan require the use of effective treatment strategies with robust improvement in resistant depression; this would curb the individual disability and socioeconomic burden prevailing because of this condition. A local study conducted in Gilgit reported rapid antidepressant effects of a single dose of ketamine in patients with severe depression. The findings showed a significant reduction in HAM-D scores 24 hours post administration of a single dose of IV ketamine. They highlighted the need to do assessments over a longer duration to establish the long-term effects of this therapy.
For any novel treatment option, it is vital to understand the patient’s experiences so their concerns can be addressed to encourage better engagement with the treatment protocol. A recent study employed qualitative interviews to identify the attitudes of patients towards ketamine therapy. Their research findings emphasised therapeutic alliance with clinicians to play an important role in improving patient acceptability of ketamine treatment. All 14 participants in this study advocated access to ketamine therapy for cases of resistant depression.

In light of limited relevant local literature, we planned our research to build a scientific database related to the immediate and sustained effects of this innovative treatment modality at our tertiary care hospital in Rawalpindi. We did not find any qualitative research in Pakistan on the subject, thus adding a qualitative component through structured interviews ensured a more in-depth understanding of the tolerability and acceptability of ketamine therapy in our patient population. The research findings provide an insight into the effective use of IV ketamine therapy in cases of treatment resistant depression.

SUBJECTS AND METHODS

This Cross-sectional study was conducted at Fauji Foundation care Hospital in Rawalpindi from January to June 2022. Ethical approval was obtained from the Institutional Ethical Review board at the study venue. Purposive sampling technique was used to approach all cases of treatment resistant depression who presented to the study coordinators during the study period. All patients 18 years and above, male or female, with a primary diagnosis of depressive episode and a Hamilton rating scale for Depression (HAM-D) score more than 19 (moderate to severe) despite 12 weeks of optimal treatment with antidepressants were included in the study. Patients with comorbid physical illnesses making them unfit for Ketamine administration were excluded from the study. We also excluded patients with substance use disorders as a safety precaution considering the abuse potential of Ketamine.

All patients received a detailed informational care session highlighting the nature of IV ketamine therapy and its status as a novel drug for treatment resistant depression. Written informed consent was obtained from each patient. A serial reference number was assigned to each case (written on their set of questionnaire booklet) and all subsequent data were handled with anonymity and confidentiality. The relevant socio-demographic details of the patients participating in the research were recorded in a specially designed data collection form. The variables included the age, gender, marital status, educational status and monthly family income. Treatment, as usual with antidepressants, was continued for all patients. All patients participating in the study were beneficiaries of the hospital and received treatment free of cost, as included in their entitlement plan.

IV ketamine was given in a sub-anaesthetic dose of 0.5mg/kg body weight in 100ml normal saline infusion over 40 minutes after an overnight fast and under supervision of an anaesthetist. Pulse, BP and digital pulse oximetry were monitored during the infusion to ensure safety. Patients were kept in recovery till fully conscious. 6 treatment sessions were administered over 2 weeks. Patients were assessed using HAM-D at 4 times during the study: A pre-treatment baseline assessment, after 1 hour of 1st dose, 2 weeks after the last dose, and a final assessment 1 month after treatment protocol. A 50% reduction in HAM-D scores at 1 hour after 1st dose was considered as treatment response. Paired t-test was applied to analyse changes in HAM-D scores over time using SPSS 26.0. A p value of <0.05 was considered as significant.

Patients were interviewed at the start and after completion of their treatment protocol regarding their attitudes and experiences related to IV Ketamine therapy. A Thematic analysis was done to identify common themes related to the tolerability and acceptability of this treatment.

RESULTS

A total of 14 patients were included in the study with age ranging from 28 to 71 years. The relevant socio-demographic details are described in Table 1.

Table 1 Socio-demographic characteristics of study participants (N=14)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>64.3</td>
</tr>
<tr>
<td><strong>Educational level</strong></td>
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<td></td>
</tr>
<tr>
<td>No formal education</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Primary education</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Secondary education</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Tertiary education</td>
<td>6</td>
<td>42.9</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Married</td>
<td>8</td>
<td>57.1</td>
</tr>
<tr>
<td>Widowed/Divorced</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Monthly Family income (in PKR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15,000</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>15-30,000</td>
<td>6</td>
<td>42.9</td>
</tr>
<tr>
<td>&gt;30,000</td>
<td>5</td>
<td>35.7</td>
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</tbody>
</table>
Table 2 shows the descriptive statistics of the clinical characteristics of patients included in the study. Failed trials of medications included the use of Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors and Selective Serotonin and Noradrenaline reuptake inhibitors. Augmentation of antidepressants was attempted with Mood stabilizers and Atypical antipsychotics in most cases. Out of all, 10 patients showed a 50% decrease in HAM-D scores when assessed 1 hour post 1st dose of treatment, thus being labelled as responders to ketamine.

The changes in HAM-D scores over time during the IV Ketamine therapy protocol are reported in Table 3. There was a statistically significant improvement in severity of depression at 1 hour and 2 weeks after the last dose of ketamine. This effect was not sustained at 1 month after the last dose.

The qualitative analysis of the data collected through structured patient interviews revealed the following major data driven themes detailed in Table 4.

### DISCUSSION

Various conventional and novel interventions are being used to manage treatment resistant depression. Our findings highlighted the role of IV Ketamine in providing rapid and significant relief in these cases at our hospital.

We found that 10 out of 14 patients in our study responded well to the 1st dose of IV Ketamine, where there was a 50% reduction in HAM-D scores 1 hour after administration of 1st dose. This is consistent with the findings of an international review article which included 20 studies for metaanalysis. The authors also reported the largest effect on severity of depression within the 1st day of administrating a single dose of ketamine. In the relevant local literature, authors of Pakistani study focusing on effects of one dose of IV ketamine shared that 12 (63.1%) patients showed a significant response to ketamine. This is similar to the findings of 10 (71.4%) Ketamine responders in our study population.

Out of all, 9 of our patients reported a failed trial of a course of Electroconvulsive therapy (ECT) prior to being included in our research; 7 of them were labelled as Ketamine responders. This indicates that Ketamine may potentially be an effective option in cases who failure to respond to ECTs, however this antidepressant effect of ketamine was not sustained after 2 weeks. A systemic review comparing Ketamine and ECT reported similar findings, where several studies suggested that ketamine exerts a more rapid antidepressant effect than ECTs. Limited data is available regarding this comparison over
weeks and months. Another study also concluded that
between-group differences in depressive symptom
improvement were significantly in favour of ketamine over
ECT, but only after the first and second treatments. 13

Some authors 14 have highlighted the potential limitations for
clinical use of Ketamine as its beneficial effects have mostly
been studied after single dose. We used a 2-week IV Ketamine
protocol where 3 sessions per week were administered to
patients. This treatment schedule was also followed by
authors of an open label study 15 in India, including 20 patients
with treatment resistant depression. Our findings are
comparable to this study, where a statistically significant
effect was seen on depression scores at 1 hour as well as 2
weeks after 1st dose.

In our study, the last assessment of severity of depression was
carried out 1 month after the last dose of ketamine. We
reported that the change in HAM-D scores from baseline to
this end point assessment was not statistically significant.
Hence, despite the initial improvement, Ketamine treatment
did not appear to have sustained effects on depressive
symptomatology after 1 month. A review article 15 also
endorsed this limitation of ketamine use, citing its transient
antidepressant effects. These findings may point towards the
need for maintenance treatment with ketamine, but the
safety and effectiveness of prolonged treatment sessions need
to be established first.

A recent narrative review 16 covered the dosing, safety, and
tolerability of IV and intranasal ketamine use. The authors
concluded that patients generally experience approximately 2
to 3 weeks of relief from severe depressive symptoms and
suicidal ideation after repeated ketamine infusions. We
did not focus directly on suicidal ideation, but a significant
reduction in severity of depression in cases of resistant
depression was seen up to 2 weeks after the completion of the
ketamine therapy protocol. The dose of treatment and
frequency of administering IV ketamine may be studied
further as an attempt to prolong its therapeutic effects.

Ever since the increasing clinical use of ketamine for treatment
resistant depression, there have been concerns related to its
misuse and dependence potential. Regarding the results of our
qualitative data analysis, we also reported ‘fear vs hope’ as one
of the major themes expressed by patients before starting
ketamine therapy. Some patients expressed worries about
becoming addicted to this treatment. A recent scoping
review 17 highlighted that ketamine is not liable to abuse in the
sub-anaesthetic doses used in treatment of depression,
though psychological measures of drug craving and long-term
follow-ups are recommended to reassure patients.

Some of our patients approached ketamine therapy hoping for
a successful ultimate solution to their frustrating treatment
journey with conventional strategies. A qualitative study
reported similar findings 18 including 13 cases undergoing
ketamine therapy where the patients sought this treatment as
a last resort, hoping to jump-start their recovery. Most
studies 9-18 have highlighted an initial high experienced by
patients along with a relaxed floaty feeling following the IV
ketamine dose. This was quite similar to the pleasant state of
detachment shared by most cases in our study after receiving
the initial infusion.

Most of our patients felt energised and better capable of
engaging in social activities following ketamine therapy. This
matches the findings of an international study 19 conducted
using focus group and survey data related to ketamine
treatment. The authors stated, patients were overall satisfied
with the improvement in their daily social functioning.

Few of our study participants experienced mild side effects
including dizziness, headache and nausea, also reported by
authors of a relevant literature review 20. Our patients found
these adverse effects to be either self-limiting or easily
managed with over-the-counter symptomatic treatment. A
retrospective review 21 also supported our findings where IV
ketamine was found to be well-tolerated and only 3.5% of
patients discontinued treatment due to side-effects.

Finally, at the end of the treatment protocol, most of the
patients stressed the need to make ketamine therapy an easily
accessible treatment for resistant depression. Patients being
transformed into advocates of ketamine treatment following
significant return to functioning has been cited by other
authors as well. 9-12

**Limitations and Recommendations**

Our study was based on purposive sampling to include a
specific group of treatment-resistant cases of depression
where IV Ketamine was indicated. The quasi-experimental
pre- and post-test design worked well for this novel treatment
in our setup, however we could not cater for randomisation
and placebo-controlled comparisons. Studies with larger
sample size and a randomised controlled method will be useful
in allowing better generalisation of findings. Despite these
important limitations, we believe our findings make a
significant contribution to the now flourishing literature on the
use of ketamine in cases of treatment resistant depression.

**CONCLUSION**

IV Ketamine therapy was found to be a rapid, effective and
acceptable tool for treatment resistant depression; though its
longer-term effects could not be established.

**Conflict of interest:** Nil

**Funding disclosure:** Nil
REFERENCES


