Ketamine as an adjunctive therapy for major depression - a randomised controlled pilot trial: The KARMA-Dep Trial

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Background and aims: Major Depressive Disorder (MDD) is the leading cause of disability worldwide. There is a need for new treatments. One novel approach is the dissociative anaesthetic ketamine. Ketamine is an antagonist of the NMDA receptor and thus targets the excitatory amino acid neurotransmitter glutamate. At sub-anaesthetic doses, single infusions of ketamine can elicit rapid, though transient, antidepressant responses.

Objectives: We aimed to conduct a pragmatic randomised controlled pilot trial of four serial once-weekly ketamine infusions as adjunctive therapy for depression. The main objective was to assess trial procedures to inform a future definitive trial.

Characteristic	Total sample n=25		Ketamine n=13		Midazolam n=12	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	50.5	12.6	48.9	13.1	52.3	12.5
BMI	28.7	5.5	28.2	7.1	29.3	3.1
Education (years)	15.9	3.4	17.1	3.9	14.7	2.2
Baseline HRSD-24	27.7	3.9	28.4	4.3	27.4	4.3
Baseline QIDS-SR 16	17.2	3.9	17.3	3.3	16.8	4.6
Baseline MOCA	26.9	1.9	26.8	2.0	27.0	1.9
Number of psychotropic meds	3.2	1.5	3.6	1.5	2.8	1.4
Treatment resistance (MSTRD)	7.4	2.1	7.8	2.5	7.0	1.5
	Median	Range	Median	Range	Median	Range
Episode duration (in days)	60	14-720	42	14-330	75	14-720
Previous number of episodes	5	1-40	5	2-40	7	1-20
Length of stay	35	8-107	37	8-107	34.5	11-63
Age of onset of depression	21	12-49	21	12-43	22	12-49

Baseline clinical and demographic characteristics

Materials and methods: Trial participants were patients admitted to St Patrick's University Hospital, Dublin, for treatment of a depressive episode (DSM-5) with a Hamilton Depression Rating Scale (HDRS-24) score ≥21. Consented participants were randomly allocated (1:1 ratio) to a four-week course of once-weekly ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) 40-minute infusions. Both groups continued treatment as usual.

Results:

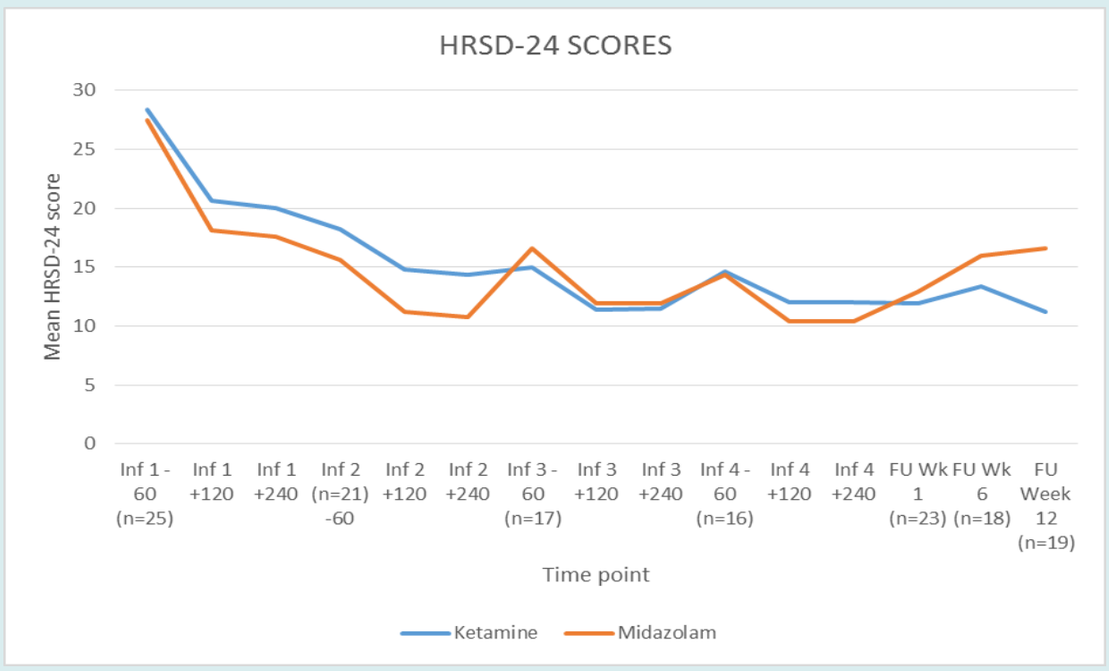
Depression scores: There were no significant differences in HRSD-24 scores between the two groups at any time point throughout the trial. There were no participants who met response criteria for HRSD-24 score during the first infusion at either time points. One week after the first infusion, one participant (1/9; 11%) responded in the ketamine group while four (4/12; 33%) met response criteria in the midazolam group. At the 12 week follow up HRSD-24 assessments, there was no significant difference between the proportion of responders in the ketamine group (7/10; 70%) and midazolam group (4/9; 44%) (odds ratio [ketamine/midazolam] = 2.9, 95% 0.42-19.2).

Physical side effects: Eight participants in the ketamine group (62%) and one participant in the midazolam group (8%) had a transient systolic BP increase of ≥20% from baseline during at least one infusion. None of these required intervention.

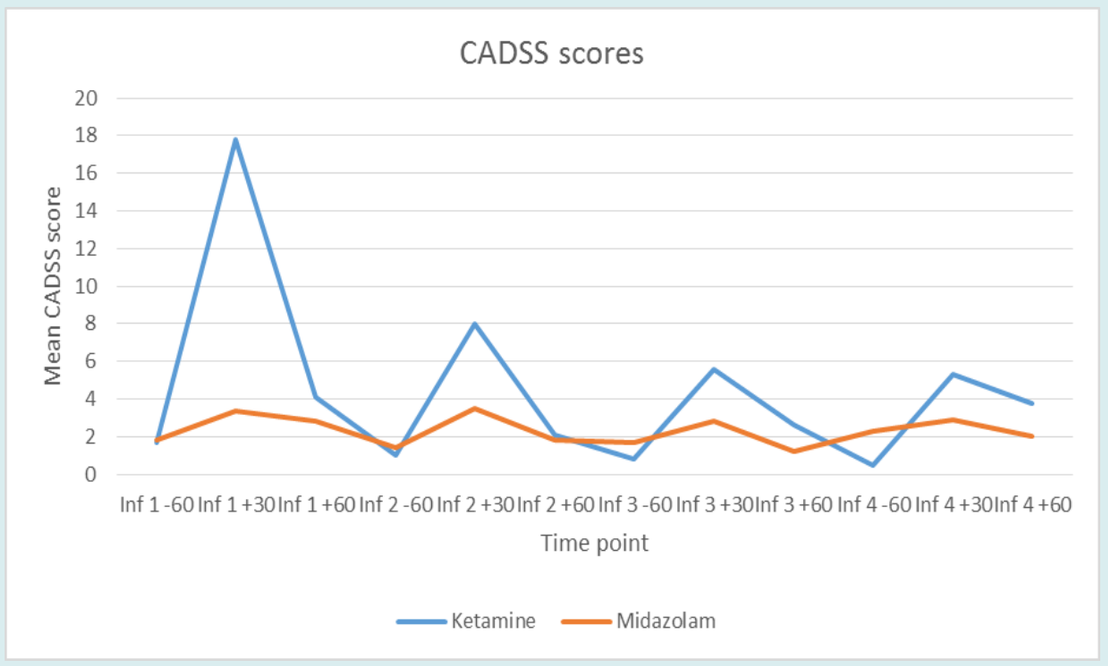
Psychotomimetic side effects: The infusions were generally safe and well tolerated by this patient population. Dissociative side-effects were greater in the ketamine group, in particular during the first infusion (t=3.20, df= 23, p=0.04), but were generally mild and transient, resolving shortly after infusions finished. The CADSS scores within the ketamine group declined with each subsequent treatment. There were no episodes of elation in either group.

Success of blinding: 77% of participants and 77% of raters correctly guessed that they received ketamine. 58% of participants and 83% of raters correctly guessed that they received midazolam.

Conclusions: This is one of the first pragmatic trial of adjunctive serial ketamine infusions for depression, an important possible use of ketamine. This study suggests that a definitive trial of adjunctive ketamine will be feasible. Ketamine was safe to use and well tolerated by the participants. 64% of participants completed all four serial infusions.



Mean HRSD-24 scores for both groups throughout the trial



Mean CADSS scores for both groups throughout the trial

Inf1=Infusion 1; Inf2=Infusion 2; Inf3=Infusion 3; Inf4=Infusion4 -60=60minutes pre-infusion 120=120 minutes into infusion 240=240 minutes into infusion FU=Follow-up Wk=week

-60=60minutes pre-infusion; 30M=30minutes into infusion; 60M=60 minutes into infusion