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Journal of Psychiatry and Mental Health
ISSN 2474-7769 | Open Access

CASE REPORT

Volume 6 - Issue 2

Intramuscular Ketamine to Treat Major Depressive Disorder: A Case Series of Forty Patients

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Received: 01 Sep, 2021 | **Accepted:** 06 Oct, 2021 | **Published:** 13 Oct, 2021

Citation: Bonnett CJ, Jain R, Ross CN, Wallington DA, Schock TR (2021) Intramuscular Ketamine to Treat Major Depressive Disorder: A Case Series of Forty Patients. J Psychiatry Ment Health 6(2): dx.doi.org/10.16966/2474-7769.145

Abstract

Introduction: While the use of ketamine to treat severe depression and post-traumatic stress disorder has been well documented in the literature, fewer studies have investigated the efficacy of Intramuscular (IM) ketamine to treat these conditions.

Methods: This case series included 40 patients with major depressive disorder who received this center's standard treatment of six IM ketamine treatments. Patients completed the Patient Health Questionnaire (PHQ-9), PTSD Checklist for DSM-V (PCL-5), and the Generalized Anxiety Disorder-7 (GAD-7) before ketamine administration and prior to the sixth session.

Results: Forty subjects (19 male, 21 female) participated in the study with a mean age of 36.9 years (range 18-67 years). On the measure of depression (PHQ-9), the mean score showed a 55% reduction, with a Cohen's *d* effect size of 1.71 ($F=84.4$, $P< 0.001$). Measurement of PTSD (PCL-5) symptoms showed a 51% decrease in mean score, with Cohen's *d* effect size of 1.61 ($F=73.4$, $P < 0.001$). The Generalized Anxiety Disorder (GAD-7) instrument showed a 51% mean score decrease, with Cohen's *d* size effect of 1.63 ($F=66.1$, $P< 0.001$).

Conclusions: The results of the series of patients presented in this series show that the immediate results of intramuscular therapy are comparable to those found using intravenous therapy.

Keywords: Patient Health Questionnaire (PHQ-9); Depression; Intramuscular ketamine

Introduction

The use of ketamine to treat severe depression and Post-Traumatic Stress Disorder (PTSD) has been well documented in the medical literature [1-8]. Many studies have looked at the use of Intravenous (IV) ketamine, but fewer have specifically looked at the use of Intramuscular (IM) ketamine to treat mental health conditions [9-11]. In order to increase access to ketamine therapy during the COVID-19 pandemic that unfolded in 2020, the centers described in this report joined the Colorado Health First network (CHF). CHF is Colorado's Medicaid program. Reimbursement rates from CHF are much lower than what was previously received with an IV cash-pay model, so it was imperative to adopt a strategy to make operations more cost effective while at the same time maintaining clinical effectiveness. In order to accomplish this, our centers converted from a treatment model based on IV ketamine to one based on IM ketamine. These operational changes resulted in a decrease in costs and an increase in the ability to provide access to psychedelic treatments to a much larger group of patients. In this case series we present our treatment results on a series of forty sequential patients who had a diagnosis of major depressive disorder and who received our new IM protocol. All patients described received our standard clinical treatment protocol as outlined in the procedures. No experimental component was added outside of the standard clinical protocol. We will discuss how these results compare favorably to both our previous published results and the results of other investigators.

Methods

Study participants

This case series describes forty sequential patients who were treated at the participating centers. All patients in this series had a diagnosis of major depressive disorder and had health first Colorado as their payor source. All of the patients received our standard treatment protocol and there was no experimental component added to their treatment plan. The mean age of the subjects was 36.9 years (range 18-67 years). There were 19 male subjects and 21 female subjects. None of the patients carried any diagnosis of psychosis.

Procedures

Each patient had an intake screening by one of our licensed mental health professionals and was determined to be an appropriate candidate for ketamine therapy. All the patients in this series already

Table 1: Individual data pre and post ketamine scores.

Individual Patient Data											
	Gender	Weight (kg)	Age	Final Dose (mg)	Final Dose (mg/kg)	PHQ-9 Score		PCL-5 Score		GAD-7 Score	
						Pre-Ketamine	Post-Ketamine	Pre-Ketamine	Post-Ketamine	Pre-Ketamine	Post-Ketamine
Patient 1	F	50	49	70	1.4	13	8	50	35	13	6
Patient 2	F	48	52	160	3.3	17	4	54	13	17	3
Patient 3	F	99	55	180	1.8	21	15	48	38	17	17
Patient 4	M	82	26	180	2.2	23	0	68	31	21	10
Patient 5	M	73	53	160	2.2	16	13	29	44	12	11
Patient 6	F	93	27	140	1.5	18	13	57	30	13	4
Patient 7	F	65	29	180	2.8	15	7	41	9	18	7
Patient 8	M	111	31	160	1.4	14	8	15	16	16	5
Patient 9	F	79	30	180	2.3	23	6	73	24	21	7
Patient 10	M	78	59	160	2.1	23	4	40	12	17	3
Patient 11	M	86	44	160	1.9	25	9	40	26	9	7
Patient 12	F	51	18	120	2.4	21	4	56	17	18	4
Patient 13	F	100	49	180	1.8	17	10	34	19	9	4
Patient 14	M	146	45	180	1.2	8	9	41	19	18	7
Patient 15	M	102	31	180	1.8	15	3	59	14	17	6
Patient 16	M	99	36	180	1.8	11	9	34	32	10	7
Patient 17	M	85	31	140	1.6	10	0	52	5	12	1
Patient 18	M	80	34	160	2	20	2	52	12	20	6
Patient 19	M	79	52	100	1.3	17	13	27	15	7	16
Patient 20	F	62	18	160	2.6	27	19	67	66	18	13
Patient 21	M	61	30	140	2.3	12	2	50	12	10	5
Patient 22	M	73	40	160	2.2	13	7	56	15	7	7
Patient 23	M	68	20	140	2.1	19	12	39	32	13	13
Patient 24	M	122	67	110	0.9	18	6	40	18	7	3
Patient 25	F	77	42	160	2.1	1	1	4	5	6	2
Patient 26	F	91	28	180	2	13	9	47	25	9	7
Patient 27	F	62	34	140	2.3	17	1	35	6	12	3
Patient 28	M	76	20	160	2.1	19	5	15	8	11	6
Patient 29	M	85	53	140	1.6	20	13	47	41	18	14
Patient 30	F	77	23	180	2.3	19	5	57	18	21	7
Patient 31	F	52	22	120	2.3	10	5	50	23	20	7
Patient 32	F	53	22	180	3.4	8	1	42	20	10	6
Patient 33	F	71	25	160	2.3	18	9	68	44	21	11
Patient 34	F	81	37	180	2.2	16	8	63	24	15	7
Patient 35	M	69	36	180	2.6	3	8	17	26	6	8
Patient 36	F	77	48	140	1.8	10	1	43	14	18	6
Patient 37	F	90	39	100	1.1	20	7	50	8	17	4
Patient 38	F	101	58	80	0.8	13	15	37	34	4	3
Patient 39	M	93	31	140	1.5	17	4	53	11	20	6
Patient 40	F	101	30	120	1.2	17	8	40	17	17	5

had an established diagnosis of major depressive disorder. Each patient had three psychological scoring instruments administered before, and at the end of an induction series of six ketamine treatment sessions. Patients were administered the patient health questionnaire (PHQ-9), PTSD checklist for DSM-V (PCL-5) and generalized anxiety disorder scale (GAD-7) prior to the first ketamine session. Just prior to each patient's sixth session the same three instruments were administered again [11-16].

The participants all received treatment according to our standard clinical protocol. Per our protocol, participants received an initial series of six IM ketamine sessions spread over three weeks. Patients started with an initial dose of 1 mg/kg with a maximum of 60 mg on the first session. The total dose is divided into two equal doses separated by fifteen minutes. If a patient appears to be having an overly profound psychomimetic experience after the first injection, then the clinician may refrain from administering the second dose, though

Table 2: Pre and post ketamine infusion scores.

Psychological Screening Instrument Results								
	Pre-Ketamine	**SD**	**Post-Ketamine**	**SD**	**F**	**P**	**Chi-Squared**	**Change**
PHQ-9	15.9	5.6	7.1	4.6	84.4	<0.001	9.3	-55%
PCL-5	44.8	15.3	22.0	12.9	73.4	<0.001	9.2	-51%
GAD-7	14.1	5.0	6.9	3.7	66.1	<0.001	9.3	-51%

Table 3: Final ketamine dose calculation.

Ketamine Doseage on Sixth Session				
	Mean	**SD**	**Median**	**Range**
Dose Calculation (mg/kg)	1.97	0.57	2.05	0.8-3.4
Final Dose (mg)	151.0	29.6	160.0	70-180

this is rare. After the first session, the dose of ketamine is increased incrementally to guide the patient to a point of enlightened experience that we refer to as the Psychotropic Therapeutic Response (PTR). This stepwise escalation is based on patient response and determined through a collaborative discussion between the providers and patients. Per protocol, the maximum dose that could be administered is 200 mg total divided into two 100mg injections spaced fifteen minutes apart.

On the first visit, each patient has his/her weight measured and recorded. During each ketamine session, patients have vital signs checked prior to administration of ketamine, which include blood pressure, heart rate, pulse oximetry and respirations. They then have repeat vital signs documented before the second injection and one hour after the first injection. During each session, patients are monitored and observed by clinical personnel while receiving ketamine. A combination of direct monitoring and observation using high-quality video cameras is utilized. The video cameras allowed for better social distancing in the context of the COVID-19 pandemic [17-20].

Results

The individual demographic, dosing and pre/post-ketamine score results for each of the 40 patients are presented in table 1. In this series, 39 of 40 patients (98%) reported improvement in their depression symptoms. Pooled data of the mean scores of each survey instrument are shown on table 2. On the measure of depression (PHQ-9), the mean score showed a 55% reduction from 15.9 to 7.1, with a Cohen's *d* effect size of 1.71 (F=84.4, P< 0.001). Measurement of PTSD (PCL-5) symptoms showed a decrease in mean score from 44.8 pre-treatment to a score of 22.0. This represents a 51% reduction, with Cohen's *d* effect size of 1.61 (F=73.4, P < 0.001). The generalized anxiety disorder (GAD-7) instrument showed a mean score of 14.1 pre-ketamine and decreased to a mean score of 6.9 after ketamine treatment. This represents a 51% decrease, with Cohen's *d* size effect of 1.63 (F=66.1, P< 0.001).

Table 3 shows the mean dosage on the final ketamine session in terms of absolute dose and in terms of milligrams per kilogram of ketamine. Throughout the six sessions we progressively increase the doses to the desired experiential effect. The mean final doses of ketamine were 151 mg in absolute dose and 1.97 mg per kilogram of body weight.

Discussion

The results of the series of patients presented in this series show that the immediate results of intramuscular therapy are comparable to those found using intravenous therapy [1-3,7,20-24]. Interestingly, our results with this series are also comparable to a previous study we published that looked at the use of intravenous ketamine to treat PTSD in a series of combat veterans [20]. In that study we demonstrated a 97% positive response rate of the veterans to ketamine therapy. The primary diagnosis in that study was PTSD however whereas in this series, it is major depressive disorder. Nonetheless it is revealing that the results are similar given that each cohort was treated in the same facilities by the same clinical staff with only the route of delivery of ketamine changed.

Other authors have demonstrated response rates for patients with severe depression treated with ketamine ranging from approximately 60-80% [21-24]. The results of this case series suggest that delivery of ketamine through an IM route does not appear to be inferior to IV ketamine. Further studies that compare IM ketamine head-to-head with both IV and a new commercially available intranasal formulation would be very valuable [16]. Additionally, longitudinal studies to look at the long-term sustainability of the antidepressant effect of IM *vs.* IV ketamine would be valuable. Given that IM ketamine can be administered in a much more cost-effective manner, these results have significant public health ramifications with regards to increasing access to psychedelic therapies such as ketamine for the treatment of mood disorders.

Acknowledgement

Candy McKenna assisted with layout, data synthesis, and proofreading.

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