Neuroscience and Biobehavioral Reviews 77 (2017) 232–236

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Meta-analysis

Ketamine as a rapid-acting agent for suicidal ideation: A meta-analysis

Francesco Bartoli[a,*], Ilaria Riboldi[a], Cristina Crocamo[a], Carmen Di Brita[a], Massimo Clerici[a], Giuseppe Carrà[a,b]

[a] Department of Medicine and Surgery, University of Milano Bicocca, Monza, Italy
[b] Division of Psychiatry, University College London, London, UK

ARTICLE INFO

Article history:
Received 21 December 2016
Received in revised form 9 March 2017
Accepted 17 March 2017
Available online 23 March 2017

Keywords:
Ketamine
Suicidal ideation
Meta-analysis

ABSTRACT

The current systematic review and meta-analysis aimed at exploring acute effects of intravenous (IV) ketamine, an antagonist of N-methyl-D-aspartate (NMDA), in subjects with current suicidal ideation. We included clinical trials testing a single IV dose of ketamine and assessing changes in suicidal ideation within 4 h after treatment. Meta-analyses based on random-effects models, were carried out generating pooled standardized mean differences (SMDs) between endpoint and baseline scores. Heterogeneity among studies was estimated using the I^2 index. We searched main Electronic Databases, identifying five studies that met our inclusion criteria. The trials included 99 subjects treated with IV ketamine bolus or infusion. Data showed a large (SMD = −0.92; 95%CI: −1.40 to −0.44; $p < 0.001$) and consistent ($I^2 = 21.6\%$) decrease of suicidal ideation, with effects comparable between IV bolus and infusion ketamine. Additional analyses confirmed the efficacy of ketamine across different time points. However, relevant, emerging evidence should be considered as 'very low' so far. Randomized, controlled and adequately powered trials are needed.

Contents

1. Introduction 233
2. Methods 233
   2.1. Eligibility criteria 233
   2.2. Search strategy and data extraction 233
   2.3. Data analysis 233
3. Results 234
   3.1. Study selection 234
   3.2. Synthesis of results 234
4. Discussion 234
   4.1. Summary of evidence and limitations 234
   4.2. Open questions and future directions 234
5. Conclusions 235
Role of funding source 235
Conflict of interest 235
Acknowledgments 235
Appendix A.Supplementary data 235
References 235

* Corresponding author at: University of Milano Bicocca, Via Cadore 48, 20900 Monza, Italy.
E-mail address: f.bartoli@campus.unimib.it (F. Bartoli).

http://dx.doi.org/10.1016/j.neubiorev.2017.03.010
0149-7634/

1. Introduction

Although approved antidepressants act through monoaminergic mechanisms, with various affinities for serotonin and noradrenaline, it has been recently hypothesized an important role for glutamate system in mood regulation (Serafini et al., 2014; Zarate et al., 2010), also in terms of target for novel therapeutic approaches (Caddy et al., 2014; Iadarola et al., 2015; Lapidus et al., 2013). In particular, ketamine, an antagonist of N-methyl-D-aspartate (NMDA), proposed for anesthesia in the 1960s, is considered a promising option for subjects suffering from severe and treatment-resistant depression (Malhi et al., 2016). Ketamine might modulate glutamatergic receptors, enhancing neuroplasticity and neurogenesis, as well as the release of neurotransmitters involved in mood regulation (Lee et al., 2015a; Serafini et al., 2015). Preliminary, though limited, evidence for ketamine and other modulators of glutamate receptors in depression treatment has been highlighted (Caddy et al., 2015). Recent meta-analytic data have shown that, in both *unipolar* and *bipolar* depression (Lee et al., 2015b), ketamine might have a significant antidepressant effect, lasting from four hours to seven days after treatment (Coyle and Laws, 2015). Moreover, although the neurobiological basis underlying the relationship between depression and suicide is not fully understood (Rajkumar et al., 2015), it seems that the rapid onset of action of ketamine, along with an acute antidepressant effect, might reduce also suicidal ideation (Malhi et al., 2016; Mallick and McCullumsmith, 2016; Wilkinson and Sanacora, 2016). Indeed, recent systematic reviews highlighted that ketamine might be effective in reducing suicidal ideation and depressive symptoms quickly, with minimal short-term side effects, though its neurobiological correlates remain to be clarified (Mallick and McCullumsmith, 2016; Reinstatler and Youssef, 2015).

However, although a body of evidence of acceptable size has accumulated in the last few years, there are no studies that systematically pooled data of intervention studies published in this field so far. Several clinical trials have investigated the effect of ketamine in subjects with treatment-resistant (Price et al., 2009; Thakurta et al., 2012) or bipolar (Zarate et al., 2012) depression, independently by the occurrence of suicidal ideation. Nonetheless, in order to increase consistency of evidence, it seems important pooling data deriving from studies including only (Ionescu et al., 2016), or separately assessing (DiazGranados et al., 2010), subjects with current suicidal ideation, rather than depression as such. Investigating novel therapeutic options for suicidal ideation is important because a significant proportion of patients still fail to respond to standard treatment approaches (Pompili et al., 2010; Stone et al., 2009) and suicide risk prevention still represents an unmet need in psychiatric clinical practice (Wilkinson and Sanacora, 2016). We thus conducted a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines-based systematic review and meta-analysis of clinical trials (Moher et al., 2009), testing early efficacy of ketamine for suicidal ideation with the purpose of clarifying the magnitude of the effect, consistency of results, as well as quality of evidence (Schünemann et al., 2008).

2. Methods

2.1. Eligibility criteria

We included clinical trials testing a single intravenous (IV) dose of ketamine for acute treatment of suicidal ideation. To be considered, studies had (i) to recruit adults with current suicidal ideation from any inpatient and/or outpatient or emergency department settings, and (ii) to assess changes in suicidal ideation with an appropriate rating instrument and within four hours after treatment, since this is the standard time point used to assess acute responses to IV ketamine (DiazGranados et al., 2010; Ballard et al., 2014). Due to the exploratory nature of this meta-analysis, neither active comparators nor placebo were required, and single-arm clinical trials testing ketamine were considered. We excluded studies dealing with treatment-resistant depression or bipolar depression, that did not provide data for subgroups of participants reporting baseline suicidal ideation, as well as studies testing suicidal ideation changes later than four hours. Furthermore, we excluded reports with incomplete data, such as conference abstracts and dissertations, and gray literature not undergoing a peer-review process. If data from the same sample had been published in multiple works, we retained for meta-analysis only the study with more exhaustive information to avoid duplicate (multiple) publication bias (Sterne et al., 2008).

2.2. Search strategy and data extraction

We searched Pubmed and, via Ovid, Medline, Embase and PsycInfo electronic databases from inception till November 2016. We used the following search phrase: *(ketamine and (suicide or suicidal ideation)).mp.* with '*mp*' code meaning that the search included title, abstract, heading word, and keyword. Furthermore, we searched reference list of two recently published systematic reviews (Mallick and McCullumsmith, 2016; Reinstatler and Youssef, 2015). After the preliminary screening based on titles and abstracts, studies were retrieved in full text in order to test their eligibility. We developed an extraction sheet for main information from each study including year of publication; study location; setting; suicidal ideation definition and assessment; sample size; participants' characteristics; tested ketamine dose and methods for IV administration (infusion or bolus); minutes between ketamine treatment and outcome measurement; main results. Systematic searches and data extraction were performed by two authors independently (IR and CDB). Discordances were resolved by consensus with other co-authors. When reported information was incomplete or unclear, one investigator (FB) contacted the relevant corresponding author for clarification.

2.3. Data analysis

We used baseline and endpoint mean scores on suicidal ideation (with standard deviations or standard errors), or relevant paired *t*-values, to estimate standardized mean differences (SMDs) with 95% confidence interval (95%CI). Because pre- and post-treatment values are dependent, effect sizes were estimated taking into account correlation between scores at different time points. Since most of studies did not include this information, we used a conservative correlation value of 0.5 (Newby et al., 2015). Individual SMDs were pooled in meta-analyses using random effects model. Statistical significance was set at $p < 0.05$. We run a subgroup analysis based on different methods of ketamine administration (infusion or bolus) and dose (0.5 mg/kg or 0.2 mg/kg), using test for subgroup differences (Deeks et al., 2008). Additional analyses were carried out to explore effect size variations at different time points, i.e., 40, 80, 120 and 230/240 min, after IV ketamine administration, according to data available from individual studies. Heterogeneity was estimated using the I^2 index, with values of 25%, 50%, and 75%, taken to indicate low, moderate, and high levels of heterogeneity, respectively (Higgins, 2003). Publication bias was assessed using Egger's linear regression test, if at least ten studies were included in the meta-analysis, as recommended (Sterne et al., 2008). Analyses were performed using STATA statistical software package (version 13.1, 2013; Stata Corp, College Station, TX).