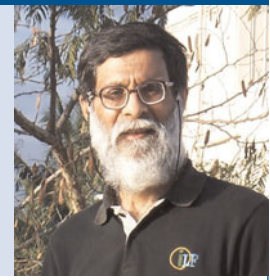


Editorial

Ketamine as anaesthesia for ECT: is there room to improve a gold standard treatment?

Chittaranjan Andrade

**Summary**

One meta-analysis of ketamine anaesthesia for electroconvulsive therapy found no improvement of end-point antidepressant outcomes; another meta-analysis with a broader range of included trials found that ketamine improved both early and late outcomes. If ketamine anaesthesia is useful, researchers may need to look for benefits earlier during the treatment course.

Declaration of interest

None.

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Ketamine, an *N*-methyl-D-aspartate receptor antagonist, has been used as an anaesthetic for about half a century. In recent years, it has also been used in subanaesthetic doses for off-label indications in children and adults; these indications include the management of post-operative pain and pain in emergency medicine settings, the management of agitation and violence in emergency medicine and other settings, and the mediation of paediatric sedation in dental, neuroimaging and other settings.¹

Outside the context of electroconvulsive therapy (ECT), in 2000 a small crossover randomised controlled trial (RCT) showed that a single subanaesthetic (0.5 mg/kg) dose of ketamine elicited an almost immediate and dramatic improvement in patients experiencing a major depressive episode.² These findings were later confirmed in patients with refractory depression in another small crossover RCT; however, the benefits were substantially attenuated within a week of dosing.³ Later studies examined the efficacy of ketamine in depression, in refractory depression, against specific symptoms of depression, as an antidepressant augmentation agent, in different doses, in serial treatment, and by different routes of administration; anecdotal reports documented successful treatment for months to years, in patients with refractory depression.¹ There is now substantial evidence for a marked, rapid onset, but short-lasting antidepressant action with subanaesthetic ketamine dosing, even in patients with severe depression who are medication refractory.⁴ The evidence, however, is insufficient to justify a label for the use of ketamine to treat depression,¹ and many issues related to safety and efficacy remain unresolved.⁵

ECT is arguably the gold standard in the treatment of severe or treatment-refractory depression, especially in patients who are suicidal or catatonic. ECT is administered under anaesthesia. The first recorded use of ketamine anaesthesia for ECT was perhaps in 1969.⁶ Ketamine anaesthesia has the advantage of lesser suppression of cough and swallowing reflexes, lesser respiratory depression, and noninterference with ECT seizure; it has the disadvantage of increasing heart rate and blood pressure.^{7,8} Given that ketamine has intrinsic antidepressant action and does not interfere with the seizure, as does barbiturate or propofol anaesthesia, might the use

of ketamine anaesthesia for ECT improve the response of depression to ECT? And how well is the combination of these two treatments tolerated? These questions were examined by McGirr *et al*⁹ in a systematic review and meta-analysis.

These authors identified ten parallel group RCTs that included patients with unipolar or bipolar depression in ketamine (0.3–2.0 mg/kg administered intravenously; $n = 333$) or control ($n = 269$) arms; ketamine was used either in monotherapy or to augment thio-pentone or propofol anaesthesia. Meta-analysis found that ketamine was not associated with greater attenuation of depression ratings in either main or sensitivity analyses, including an analysis of trials where ketamine had not been coadministered with barbiturate anaesthesia. Response rates (53.9 *v.* 53.4%; seven RCTs; $n = 339$) and remission rates (16.8 *v.* 18.9%; seven RCTs; $n = 339$) were surprisingly low and did not differ significantly between ketamine and control groups. Ketamine was associated with increased odds of confusion (odds ratio, 6.01; 95% CI, 1.03–94.30). There was some statistical heterogeneity in various analyses, but no evidence of publication bias.

Some points here are worthy of note. Of the ten RCTs, only two Asian studies^{10,11} showed a statistically significant efficacy advantage for ketamine. In both RCTs, anaesthesia dosing was inadequate or barely adequate by conventional standards, and one¹⁰ was poorly described, possibly single-blind, and had other methodological shortcomings. However, these were the two largest RCTs in the meta-analysis, with sample sizes of 160¹⁰ and 90.¹¹ The third largest ECT in the meta-analysis,¹² in stark contrast, found ketamine significantly inferior to control treatment. Given that a large, well-designed, well-conducted, and well-analysed RCT provides higher quality evidence than meta-analysis, and given that only one RCT¹⁰ had clear methodological shortcomings, the contrasting findings are a puzzle. A geographical effect for the favourable outcomes with ketamine is possible; however, there were several other Asian studies in the meta-analysis that failed to show an advantage for ketamine.

Looking more closely, the response rates in 3 RCTs, at the end of the course of ECT, were 0 out of 31, 4 out of 18, and 4 out of 45 patients. In 4 RCTs, remission rates were 0 out of 31, 0 out of 45, 2 out of 19, and 3 out of 90 patients. No RCT had a remission rate that touched 40%. In contrast, in a recent meta-analysis,¹³ the response and remission rates with ECT were 64 and 53%, respectively. This implies that there was something atypical about the patients in the ketamine versus control RCTs, in the way ECT was delivered, and/or in the way the RCTs were conducted; if so, can the findings of the meta-analysis be generalised to everyday practice? One small ($n = 40$) RCT, not included in the meta-analysis, has just been published.¹⁴ This RCT found no advantage for ketamine versus

See McGirr *et al*, June 2017.

propofol anaesthesia for ECT; depression scores attenuated substantially but response and remission rate data were not presented.

Complicating the picture is a very recent systematic review and meta-analysis on the same subject, but with somewhat broader study selection criteria; this meta-analysis (with 16 RCTs; 346 patients in the ketamine anaesthesia arm and 329 controls) additionally examined early outcomes and found a clear advantage for add-on ketamine anaesthesia at 1–2 week assessments and also at 3–4 week assessments, and in several subgroup and sensitivity analyses.¹⁵ Whereas the authors in that meta-analysis¹⁵ were certainly flexible in accommodating certain RCTs, McGirr *et al*⁹ did not examine early outcomes, may have missed some RCTs, and may have excluded others RCTs without sufficient justification.

Readers may note that, in the McGirr *et al*⁹ meta-analysis, the finding of greater confusion with ketamine was driven by one RCT;¹⁶ however, other reviews^{8,15} have reported the same results, so the finding does not bear challenge.

The studies in the meta-analysis⁹ were clinically heterogeneous regarding the ketamine dose, the nature and dose of the concomitant anaesthetic drug (if any), the severity of depression and extent of antidepressant drug resistance, electrode placement, electrical dosing and other methodological matters. One hopes that there will eventually be a sufficiently large number of studies on the subject available for adequately powered metaregression analysis to identify variables that moderate the efficacy outcomes; however, one metaregression of a broader set of RCTs failed to identify clinically important treatment variables.¹⁵

The meta-analysis⁹ examined end-point outcomes and not the possibility that ketamine may accelerate recovery as at least one large study¹¹ and several small studies suggested. It is important for future research to consider whether ketamine anaesthesia has early antidepressant effects because there certainly seems to be a signal here.⁸ However, the absence of a consistent signal favouring end-point outcomes with ketamine is disappointing. What might be the explanations?

One possibility is that the effect of ketamine is cancelled by ECT, but this cannot be asserted when at least some data suggest that ketamine improves the early response to ECT.^{8,11} Another explanation is that, by the time the ECT course completes, a ceiling effect comes into play; however, given the low response and remission rates in the RCTs, this cannot be asserted.

One wonders whether ketamine sessions on days that ECT is not administered might yield better treatment gains; for example, one small RCT found that a single ketamine session improved outcomes with escitalopram.¹⁷ However, that is an entirely different research question meriting separate consideration. If ECT is a gold standard treatment for depression, can one improve the gold standard? If yes, where might improvement be possible? Not in end-point outcomes, perhaps, because these are expected to be very good. Focusing on the early time course of response, or on time to response and remission, might be a better idea. At present, whereas the risk of confusion as an adverse outcome is perhaps increased, the efficacy data are insufficient for firm guidance regarding the use of ketamine in ECT anaesthesia. Readers who wish to take the discussion further are referred to an extensive qualitative review.⁸

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