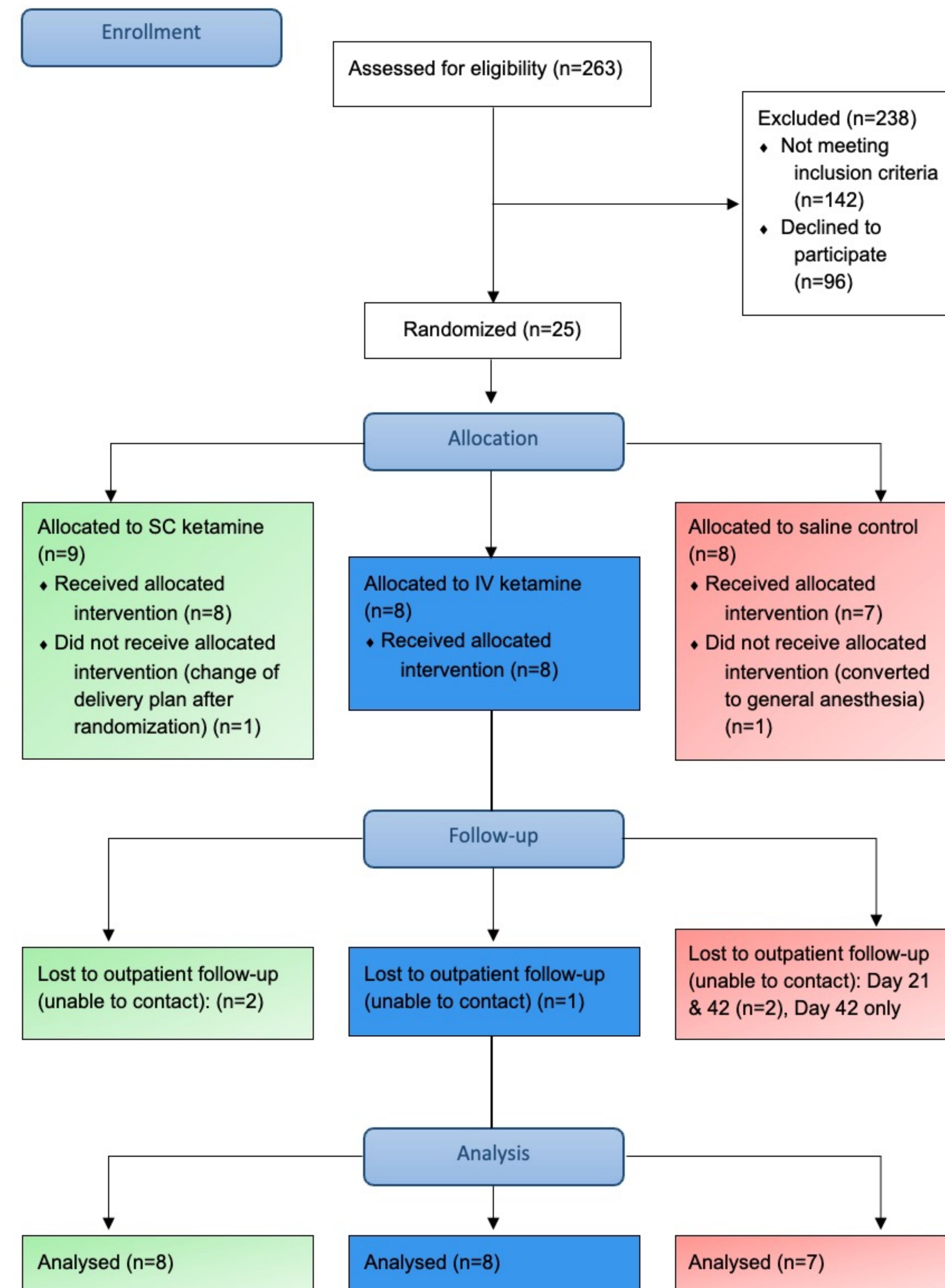


Ketamine to prevent postpartum depression after planned cesarean delivery under neuraxial anesthesia

A randomized feasibility pilot-study of intravenous and subcutaneous administration

Monks DT, Palanisamy A, Jaffer D, Singh PM, Carter EB, Lenze S. Washington University in St. Louis

Background: Postpartum depression complicates 6-19% of pregnancies.^{1,2} There is a substantial financial burden to society with an estimated annual cost of \$2.8 billion in the USA.³ Evidence suggests ketamine may prevent postpartum depression after cesarean delivery although intolerability and inconvenience of administration are problematic. A series of RCTs has suggested a benefit from ketamine, most pronounced when administered as a 2-day IV infusion, although a nauseating effect was also observed.⁴⁻⁷ We assessed the feasibility of studying ketamine (0.5 mg/kg, via subcutaneous injection or 40-minute intravenous infusion) to prevent Postpartum depression after cesarean delivery .



Methods: Twenty-three women scheduled for cesarean delivery under neuraxial anesthesia were randomized to one of three groups: subcutaneous ketamine (SC Group, n = 8), intravenous ketamine (IV Group, n = 8) or placebo (n = 7). We measured depression (Edinburgh Postpartum Depression Scale [EPDS]) scores pre-operatively and at 1, 2, 21 and 42 days postoperatively. Anxiety, adverse effects, surgical site pain and analgesic consumption were also assessed. Feasibility was assessed based on acceptability, burden of disease, ability to collect study data and, tolerability of interventions.

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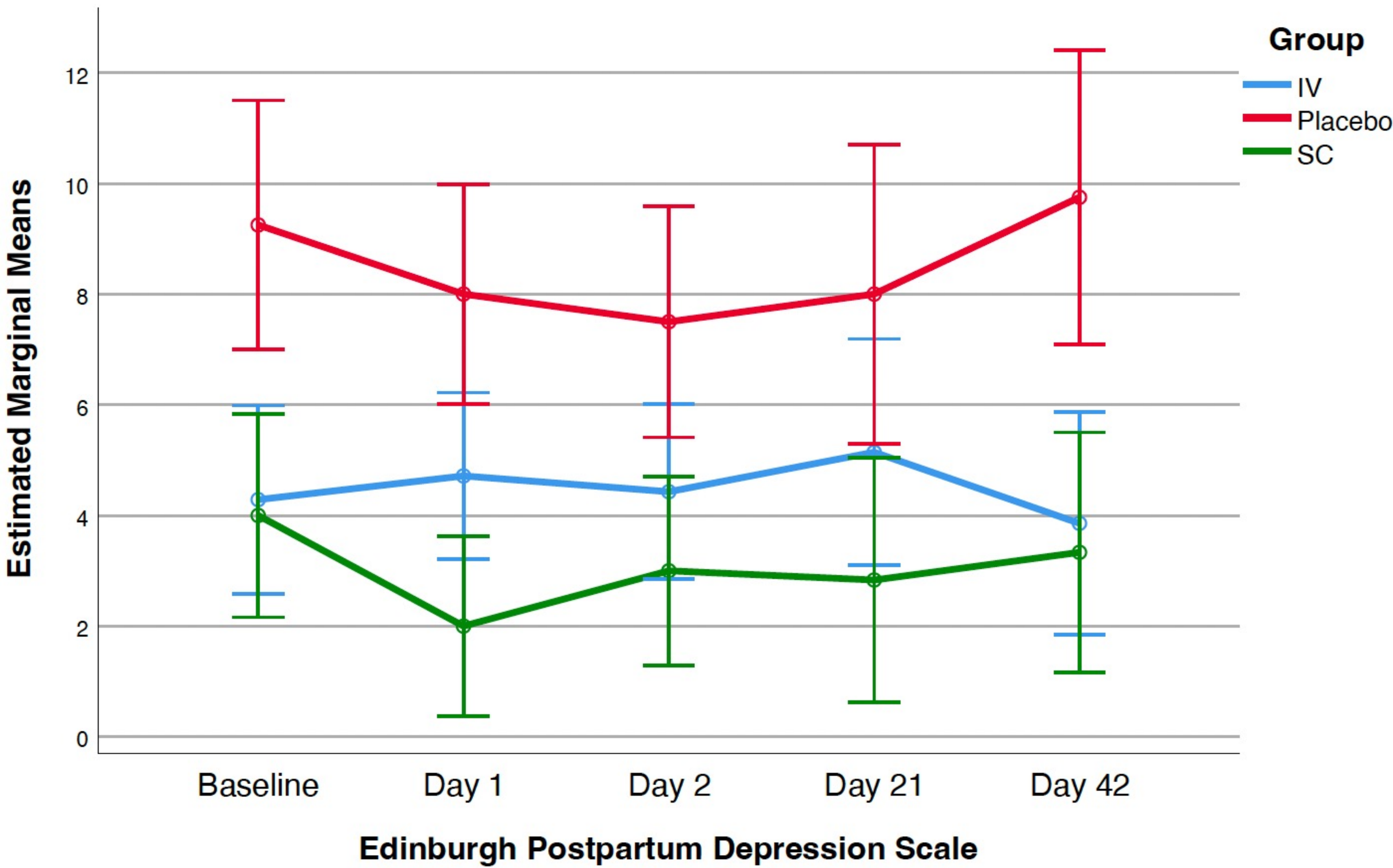
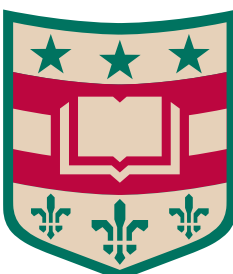
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Results: Baseline characteristics of groups were similar, however, more women in the placebo group had pre-existing anxiety disorder ($p = 0.03$). 20.7% (25/121) of those approached consented to participate and 34.8% (8/23), of those assessed, screened positive for depression in the postpartum (EPDS > 12). PPD screening data was complete in 78.3%. No differences were observed for any adverse effect outcomes except for fewer incidences of intraoperative shivering with ketamine (SC: 25%, IV: 0% and Placebo: 85.7%, $p = 0.01$). A statistically insignificant difference in positive screening for PPD was observed (SC: 14.3%, IV: 50% and Placebo: 42.9%, $p = 0.58$).

Table 1. Adverse effects					
		SC group (n = 8)	IV Group (n = 8)	Placebo (n = 7)	p-value*
Self-reported AE incidence					
		6 (75.0)	6 (75.0)	7 (100)	0.78
Nausea					
	Mild	2 (25.0)	1 (12.5)	0 (0)	0.53
	Moderate	0 (0)	3 (37.5)	2 (28.6)	
	Severe	0 (0)	0 (0)	0 (0)	
Vomiting					
	Mild	2 (25.0)	0 (0)	0 (0)	0.41
	Moderate	1 (12.5)	1 (12.5)	1 (14.3)	
	Severe	0 (0)	0 (0)	0 (0)	
Shivering					
	Mild	1 (12.5)	0 (0)	6 (85.7)	0.01**
	Moderate	1 (12.5)	0 (0)	0 (0)	
	Severe	0 (0)	0 (0)	0 (0)	
Sedation					
	Mild	1 (12.5)	2 (25.0)	1 (14.3)	0.38
	Moderate	0 (0)	1 (12.5)	2 (28.6)	
	Severe	0 (0)	0 (0)	0 (0)	
Blurred vision					
	Mild	1 (12.5)	3 (37.5)	1 (14.3)	0.41
	Moderate	0 (0)	0 (0)	0 (0)	
	Severe	0 (0)	0 (0)	0 (0)	
Diplopia					
	Mild	0 (0)	1 (12.5)	1 (14.3)	0.99**
	Moderate	0 (0)	0 (0)	0 (0)	
	Severe	0 (0)	0 (0)	0 (0)	
Dizziness					
	Mild	1 (12.5)	3 (37.5)	1 (14.3)	0.41
	Moderate	0 (0)	0 (0)	0 (0)	
	Severe	0 (0)	0 (0)	0 (0)	
Anxiety					
	Mild	0 (0)	1 (12.5)	2 (28.6)	0.23**
	Moderate	0 (0)	0 (0)	1 (14.3)	
	Severe	0 (0)	0 (0)	0 (0)	
Pruritus					
	Mild	4 (50.0)	0 (0)	1 (14.3)	0.53
	Moderate	0 (0)	2 (25.0)	1 (14.3)	
	Severe	0 (0)	0 (0)	0 (0)	
Euphoria, Amnesia, Hallucinations, Nystagmus					
		0 (0)	0 (0)	0 (0)	

	SC group (n = 8)	IV Group (n = 8)	Placebo (n = 7)	p-value*
Hemodynamic Adverse Effects				
Hemodynamic AE incidence				
	3 (37.5)	3 (37.5)	2 (28.6)	0.92
Systolic Blood pressure				
< 80 mmHg	2 (25.0)	1 (12.5)	1 (14.3)	0.78
> 170 mmHg	0 (0)	1 (12.5)	1 (14.3)	0.68
Heart Rate				
< 40 bpm	0 (0)	2 (25.0)	0 (0)	0.70
> 120 bpm	1 (12.5)	1 (12.5)	0 (0)	0.99



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Discussion: Across all groups, there was a high burden of disease. Almost 35% of women screened positive for postpartum depression (EPDS > 12). Only 20.7% of eligible patients consented to participate. This low level of acceptability of the study will have undoubtedly been affected by some of the changes to clinical care and conduct of research that were necessary during the Sars-CoV-2 pandemic.

This study was limited in its ability to assess neonatal safety outcomes.

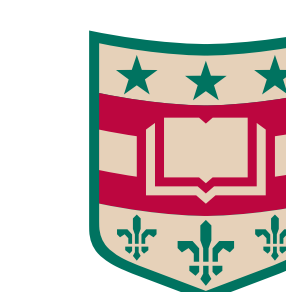
Encouragingly, early data suggests that IM administration of doses up to 1.0 mg/kg of ketamine do not pass into the breast milk to a clinically significant extent.⁸ We found no evidence of intolerability of ketamine. There were no severe adverse effects experienced by patients receiving ketamine by either route. In fact, there was a reduction in shivering in the ketamine groups compared to the control, a finding that is in keeping with previous studies.⁹

Although there is evidence of antidepressant benefit of a 2-day IV infusion of ketamine (0.01-0.08 mg/kg/hr) after cesarean, these studies are exclusively from Chinese institutions (potentially limiting generalizability) and this is impractical for most of our patients given their reluctance for prolonged IV access. Reproduction of its benefit in other populations is necessary and subcutaneous administration could provide more convenient.

Conclusion: An RCT was judged to be feasible and there was no evidence of intolerability of either route of ketamine administration.

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