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Introduction

- Ketamine provides opioid-sparing analgesia but causes emergence reactions such as hallucination, agitation, or delirium.
- Midazolam is commonly co-administered as it reduces ketamine-related agitation and may offer neuroprotection.
- Recent studies show ketamine increases 30-day psychiatric diagnoses after orthopedic surgery.
- No prior study has examined whether midazolam reduces these psychiatric risks.
- This study compares emergence and psychiatric outcomes between ketamine alone and ketamine + midazolam

Materials and Methods

Retrospective Cohort Study using TriNetX Database on patients undergoing first time orthopedic surgery:

Cohorts

1. Ketamine only
2. Ketamine + midazolam
3. Controls

Propensity score matching was performed separately for each outcome analysis, resulting in different sample sizes for each cohort

Exclusions:

- Prior psychiatric/neurodevelopmental disorders or chronic pain syndromes
- Postoperative cardiac events

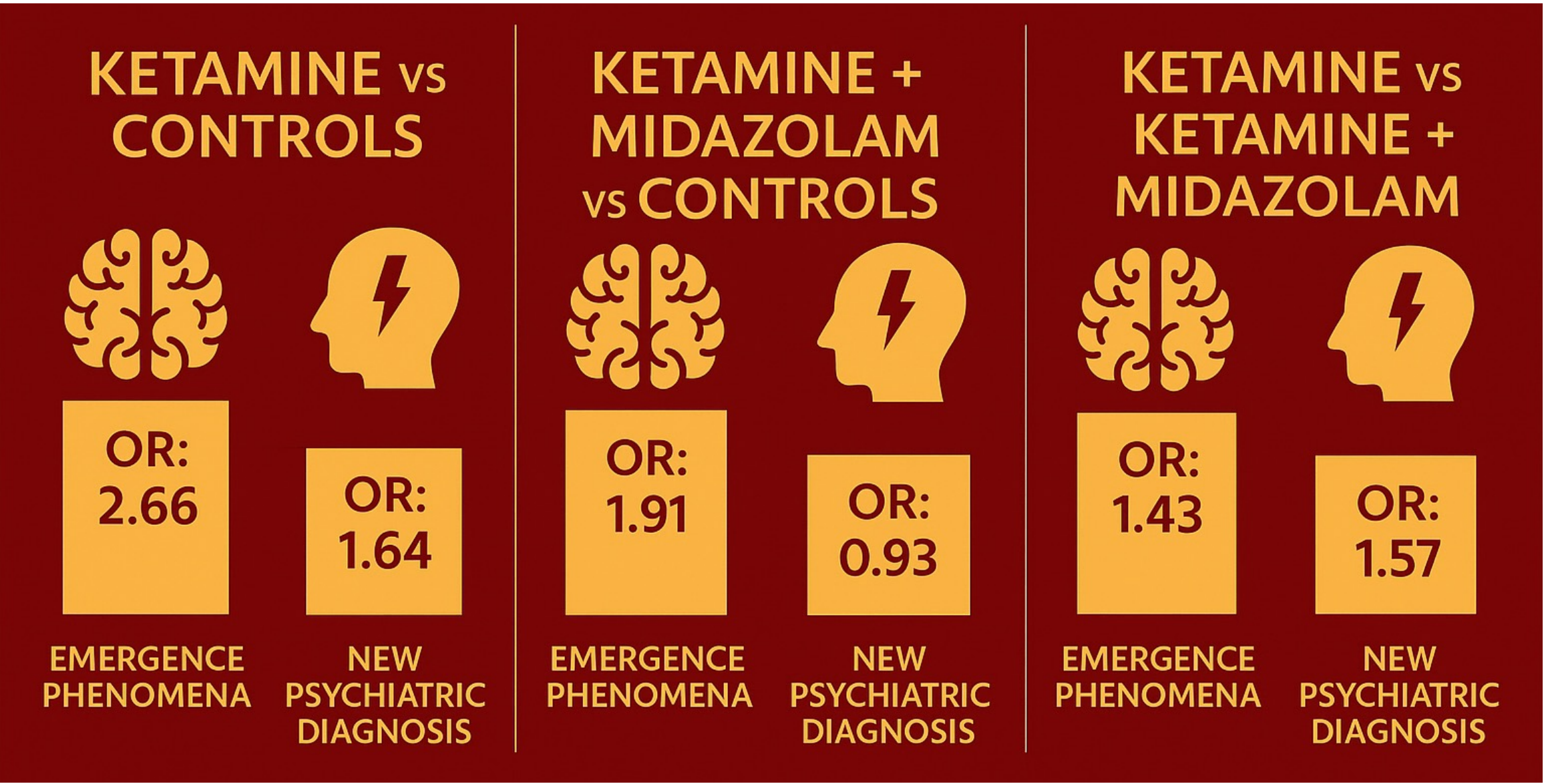
Outcomes:

- Emergence phenomena (0–1 days)
- New psychiatric diagnoses (0–30 days)

Statistical Analysis:

- Propensity score matching (1:1)
- OR with 95% CI, P<0.05
- Subgroup analyses across age groups: pediatric (≤17 years), adults (18–60), and older adults (≥61 years).

Results



Ketamine Only versus Control					
Outcome	Group	N (Ketamine)	N (Control)	OR (95% CI)	P
Emergence Phenomena	All	1,403	533	2.66 (2.41, 2.94)	< 0.0001*
	Pediatric	154	52	2.96 (2.16, 4.06)	< 0.0001*
	Adult	771	225	3.52 (3.03, 4.09)	< 0.0001*
	Older Adult	422	229	1.85 (1.57, 2.18)	< 0.0001*
Psychiatric Diagnoses	All	1,002	646	1.64 (1.49, 1.82)	< 0.0001*
	Pediatric	64	62	1.03 (0.73, 1.47)	0.8513
	Adult	645	342	2.23 (1.95, 2.55)	< 0.0001*
	Older Adult	348	210	1.78 (1.50, 2.12)	< 0.0001*

Ketamine with Midazolam versus Control					
Outcome	Group	N (K w/ M)	N (Control)	OR (95% CI)	P
Emergence Phenomena	All	2,268	1,198	1.91 (1.78, 2.04)	< 0.0001*
	Pediatric	148	32	4.67 (3.19, 6.85)	< 0.0001*
	Adult	1,502	691	2.20 (2.01, 2.41)	< 0.0001*
	Older Adult	604	433	1.36 (1.20, 1.54)	< 0.0001*
Psychiatric Diagnoses	All	518	481	0.93 (0.87, 1.00)	0.0421*
	Pediatric	148	49	3.10 (2.24, 4.29)	< 0.0001*
	Adult	1,433	1,301	1.21 (1.12, 1.31)	< 0.0001*
	Older Adult	518	481	1.14 (1.00, 1.29)	0.0443

Ketamine Only versus Ketamine with Midazolam					
Outcome	Group	N (Ketamine)	N (K w/ M)	OR (95% CI)	P
Emergence Phenomena	All	401	256	1.43 (1.31, 1.55)	< 0.0001*
	Pediatric	75	109	0.68 (0.51, 0.92)	0.0108*
	Adult	771	478	1.63 (1.46, 1.83)	< 0.0001*
	Older Adult	401	256	1.61 (1.37, 1.89)	< 0.0001*
Psychiatric Diagnoses	All	975	639	1.57 (1.42, 1.73)	< 0.0001*
	Pediatric	31	107	0.28 (0.19, 0.42)	< 0.0001*
	Adult	645	364	1.92 (1.68, 2.19)	< 0.0001*
	Older Adult	332	240	1.42 (1.20, 1.68)	< 0.0001*

Discussion & Recommendations

- Ketamine increases emergence reactions and psychiatric diagnoses.
- Midazolam attenuates these risks—especially in adults and older adults.
- Midazolam in conjunction with Ketamine may have protective effects against neuropsychiatric sequelae from ketamine-associated neurotoxicity
- Pediatric patients show opposite trends: midazolam may increase the risk of emergence phenomena and new psychiatric diagnosis when compared to ketamine only. Prior studies have also described paradoxical reactions when used with ketamine in pediatric populations. Safety of midazolam in pediatric population requires further investigation.
- An individualized assessment of patient-specific factors such as age and psychiatric history are crucial when considering ketamine for perioperative sedation and analgesia

References

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