

Double NMDA Antagonist Regimen for Elective Complex Spine Surgery Results in Reduced Total Opioid Burden and Hospital Length of Stay

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Background

Complex spine surgery is associated with:

- Severe postoperative pain
- High opioid requirements
- Prolonged hospital length of stay (LOS)

Using two or more NMDA antagonists may produce synergistic opioid-sparing effects by:

- Reducing central sensitization
- Decreasing opioid tolerance and hyperalgesia

Evidence supporting dual NMDA antagonist (D-NMDA) strategies is emerging but remains limited in real-world practice.

Objective

To evaluate whether an intraoperative D-NMDA antagonist regimen for complex spine surgery is associated with:

- Reduced postoperative opioid consumption
- Shorter hospital length of stay

Methods

Study Design

Single-institution retrospective cohort from January 2024 – January 2026

Population

Adult patients undergoing elective complex spine surgery, defined as:

- ≥6 vertebral levels fused or
- Operative duration ≥ 6 hours or
- Designated complex deformity procedures

Exposure

D-NMDA regimen:

- Intravenous methadone prior to incision
- AND
- ≥1 additional NMDA-modulating agent:
 - Ketamine, lidocaine, or magnesium sulfate infusion

Primary Outcomes

- Total opioid consumption on postoperative day 3 (MME)
- Hospital length of stay

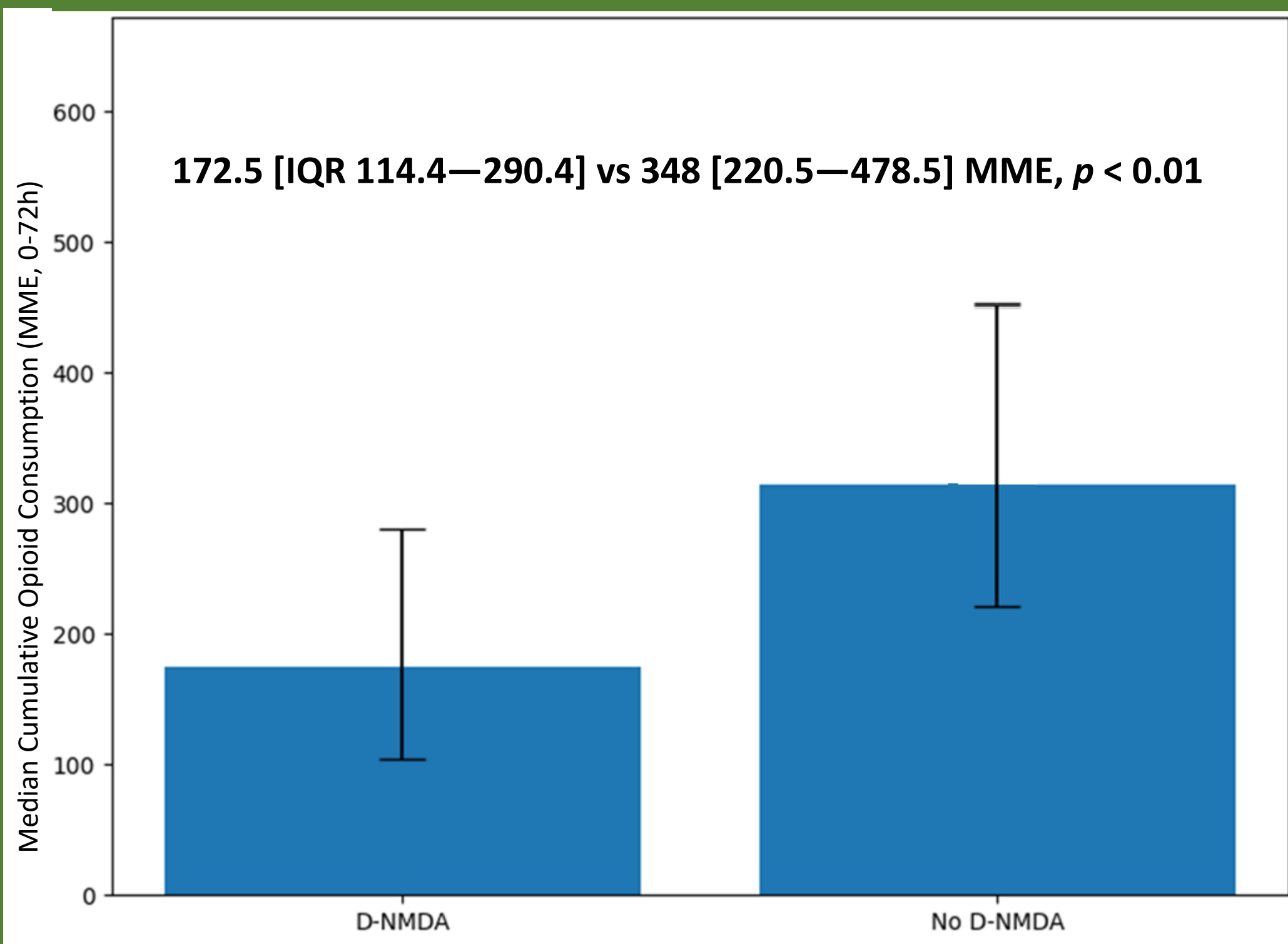
Table 1. Baseline Patient and Surgical Characteristics by D-NMDA Antagonist Exposure			
	Exposed Group (n=18)	Unexposed Group (n=69)	p-value
Age	67.0 [56.5–74.0]	65.0 [57.0–71.0]	0.46
BMI	27.9 ± 5.4	28.5 ± 5.7	0.72
Sex			0.36
Male	10 (55.6%)	30 (43.5%)	
Female	8 (44.4%)	39 (56.5%)	
Race			0.34
White	14 (77.8%)	62 (89.9%)	
Non-White	4 (22.2%)	7 (10.1%)	
ASA Class			0.14
I	0 (0.0%)	1 (1.4%)	
II	11 (61.1%)	25 (36.2%)	
III	6 (33.3%)	42 (60.9%)	
IV	1 (6.7%)	1 (1.4%)	
Preoperative MME	0.0 [0.0–28.1]	0.0 [0.0–20.0]	0.69
Smoking	3 (13.3%)	14 (20.3%)	1.00
Hypertension	12 (66.7%)	46 (66.7%)	1.00
Diabetes mellitus	3 (16.7%)	9 (13.0%)	0.71
CKD	1 (5.6%)	1 (1.4%)	0.37
OSA	8 (44.4%)	12 (17.4%)	0.03*
COPD	2 (11.1%)	10 (14.5%)	1.00
Atrial fibrillation	3 (16.7%)	9 (13.0%)	0.71

ASA, American Society of Anesthesiologists Class; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; D-NMDA, double N-methyl-D-aspartate; OSA, obstructive sleep apnea. An * denotes statistical significance.

Table 2. Perioperative Data by D-NMDA Antagonist Exposure			
	Exposed Group (n=18)	Unexposed Group (n=69)	p-value
Levels involved	10.0 ± 4.8	12.7 ± 4.6	0.05
MME 0–24 hrs	49.5 [31.9–135.8]	124.0 [76.0–177.0]	0.008*
MME 24–48 hrs	57.5 [21.9–84.1]	89.4 [55.0–127.5]	0.03*
MME 48–72 hrs	41.25 [30.0–71.3]	90.0 [45.0–120.0]	0.002*
Cumulative MME 0–72 hrs	172.5 [114.4–290.4]	348 [220.5–478.5]	<0.001*
PACU LOS, mins	145.0 [114.3–202.75]	184.0 [138.0–235.0]	0.14
Hospital LOS, days	4.2 [3.2–6.3]	6.2 [5.0–7.3]	0.042*
Total intraop fentanyl, mcg	0.0 [0.0–100.0]	100.0 [50.0–150.0]	0.05
Total intraop hydromorphone, mg	0.5 [0.0–0.9]	1.0 [0.5–1.0]	0.01*
Ketamine used intraoperatively	18 (100%)	39 (56.5%)	<0.001*
Pain score 6h postop	4.0 [3.0–7.0]	7.0 [5.0–8.0]	0.42
Pain score 12h postop	4.5 [3.3–6.0]	6.0 [4.0–8.0]	0.11
Pain score 24h postop	4.0 [3.0–5.0]	7.0 [5.0–8.0]	<0.001*
Pain score 48h postop	5.5 [3.3–7.0]	7.0 [4.0–8.0]	0.16
Antiemetic used in PACU	2 (11.1%)	12 (17.4%)	0.73
Antiemetic used inpatient	6 (33.3%)	39 (56.5%)	0.08
Rescue naloxone use	0 (0.0%)	0 (0.0%)	1.00

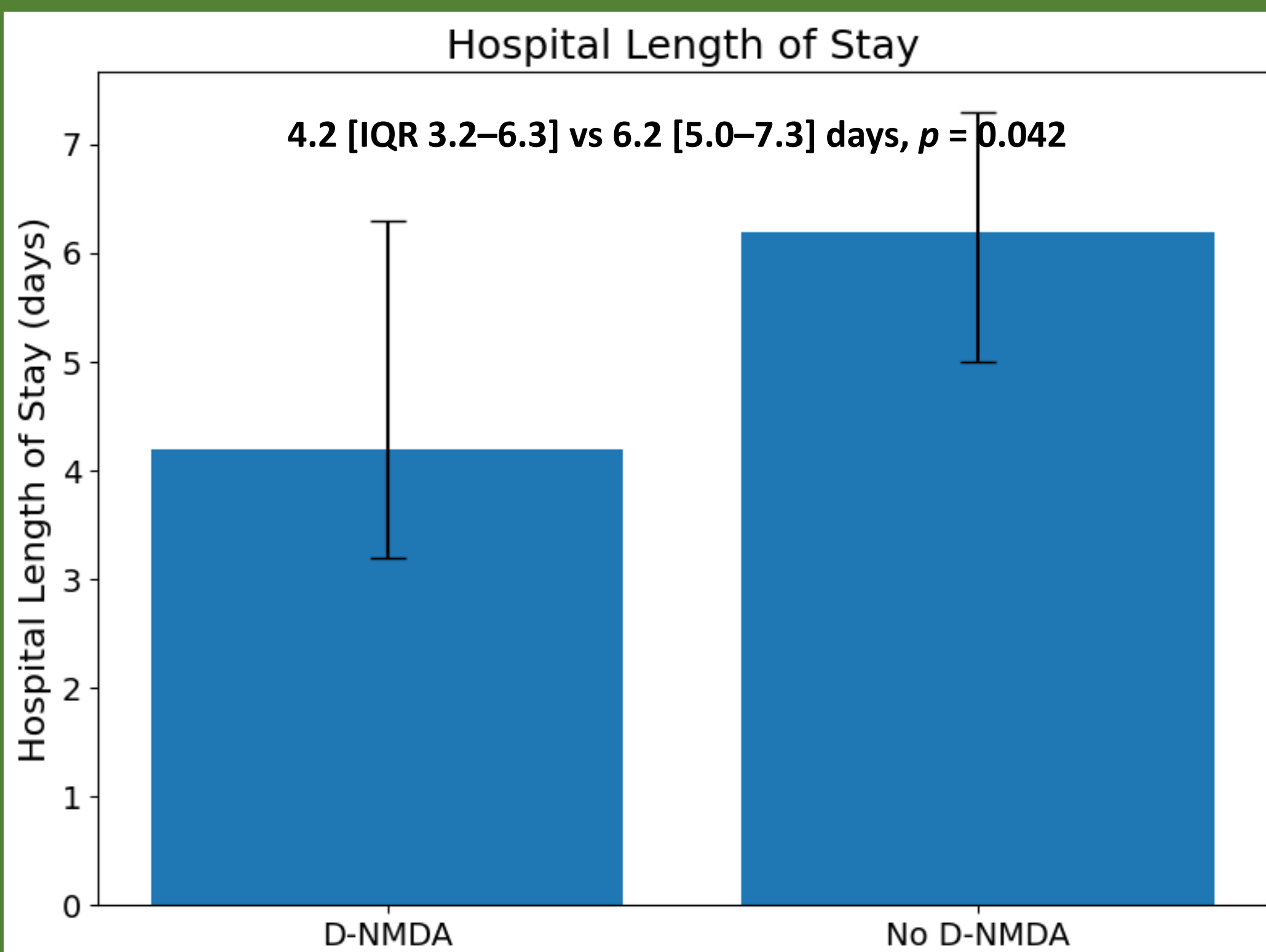
D-NMDA, double N-methyl-D-aspartate; LOS, length of stay; MME, morphine milligram equivalents; PACU, Post-Anesthesia Care Unit; PCA, patient-controlled analgesia. An * denotes statistical significance.

Figure 1: Cumulative Opioid Consumption by Postoperative Day 3



Patients who received a D-NMDA regimen demonstrated significantly lower median cumulative opioid consumption during the first 72 postoperative hours.

Figure 2: Hospital Length of Stay



Median hospital length of stay was significantly shorter among patients who received the D-NMDA regimen compared to the unexposed group

Discussion

1. D-NMDA regimen was associated with:

- Marked reductions in opioid use
- Shorter hospital length of stay

2. Opioid reduction persisted into the late postoperative period, suggesting improved analgesic durability.

3. Findings align with prior studies supporting ketamine-based multimodal strategies.

4. Benefits observed without increased respiratory or opioid-related complications

Safety and Recovery Outcomes

No difference in:

- PACU length of stay
- PCA duration
- Postoperative ketamine duration
- Antiemetic use
- Naloxone administration

Limitations

- Retrospective design
- Small exposed cohort (n = 18)
- Potential for unmeasured confounders
- Single-center study

Conclusions

A D-NMDA antagonist regimen in complex spine surgery:

- Significantly reduced postoperative opioid requirements
- Associated with shorter hospital length of stay
- No increase in opioid-related adverse events

These findings support continued protocolization and prospective evaluation of D-NMDA strategies within enhanced recovery pathways.

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