

Unexpected Rapid-Onset Tonic-Clonic Events Following Intravenous Tramadol Dose for Postsurgical Pain

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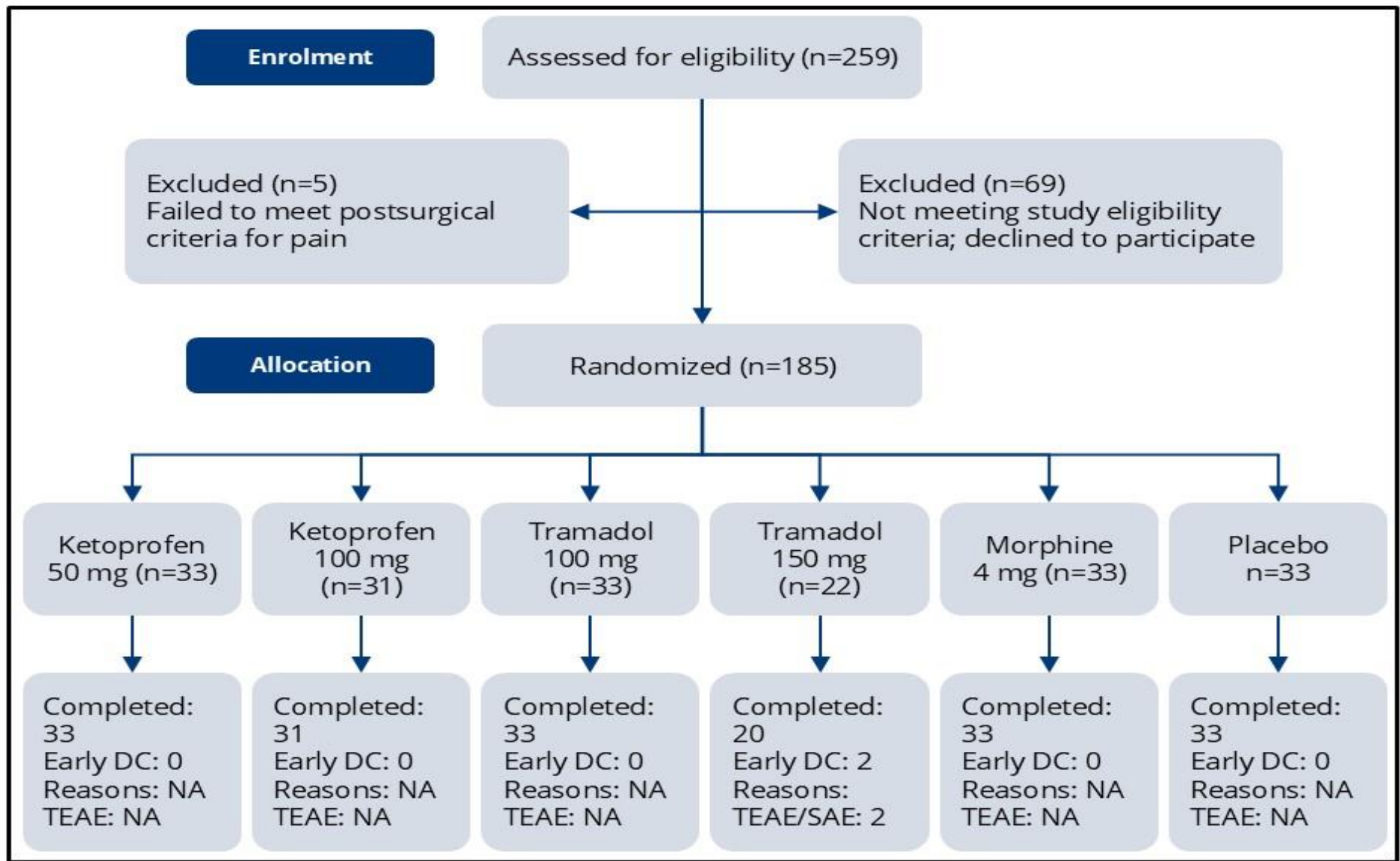
Background

Seizures are common, with about 10% of people experiencing at least one in their lifetime. Up to 30% are provoked by acute, identifiable and typically isolated triggers such as CNS infections, head trauma, metabolic disturbances, alcohol withdrawal, or drug exposure. **Intravenous tramadol is widely used outside North America for postsurgical pain.** It provides analgesia through weak μ-opioid receptor agonism and monoaminergic reuptake inhibition. Although generally considered safe, tramadol has been associated with seizures, even at therapeutic doses.

Objectives

To report two cases of rapid-onset tonic–clonic seizures in an RCT following IV tramadol 150 mg given for postsurgical pain after **extraction** of bony impacted mandibular third molars.

Study Design



Inclusion Criteria

Adults in good general health undergoing with moderate to severe postsurgical pain elective extraction of ≥2 third molars.

Exclusion Criteria

History of epilepsy or seizure disorder, raised intracranial pressure, uncontrolled chronic disease, recent substance abuse or alcohol use, or use of medications that lower seizure threshold (e.g., antidepressants, neuroleptics, opioids, sedatives).

Results

Two participants receiving IV tramadol 150 mg experienced rapid-onset generalized tonic–clonic seizures within 3–4 minutes of bolus dosing, lasting 3–5 minutes. Seizures required supportive care and were considered life-threatening. Overall, 2 of 22 subjects (9%) receiving tramadol 150 mg experienced seizures, while no seizures occurred with tramadol 100 mg or IV ketoprofen. This dose was discontinued from the RCT. Tramadol 150 mg showed no analgesic advantage over 100 mg, whereas IV ketoprofen 50 and 100 mg demonstrated greater analgesic efficacy with fewer AEs.

Feature	Case 1	Case 2
Age / Sex	30-year-old male	23-year-old female
Surgery type	Third molar extraction (partial bony impaction)	Third molar extraction (complete + partial bony impaction)
Tramadol dose	IV 150 mg	IV 150 mg
Time to seizure	4 minutes	3 minutes
Seizure type	Generalized tonic-clonic	Generalized tonic-clonic
Severity	Life-threatening	Life-threatening
Outcome	Spontaneous recovery, study withdrawal	Spontaneous recovery, study withdrawal

Table 1. Clinical characteristics and seizure events following single-dose IV tramadol.

Putative Mechanisms of Seizures

• Inhibition of GABAergic pathways

- ↓ Reduced inhibitory neurotransmission
- ↓ Lowered seizure threshold

• Histamine H1 receptor activation

- ↑ Neuronal excitability

• Opioid-linked proconvulsant effects

- μ-opioid receptor modulation may alter cortical excitability

• Serotonergic and noradrenergic effects

- Enhanced monoaminergic activity

• Rapid IV bolus administration

- High Cmax may lower seizure threshold
- Increased risk of acute seizure onset

Outcome	IV Tramadol 150 mg	IV Tramadol 100 mg	IV Ketoprofen (50–100 mg)
Analgesic efficacy	Not superior to 100 mg	Effective	Superior analgesia vs tramadol
Seizures	2 cases	0 cases	0 cases
Respiratory adverse events	15 events	6 events	Fewer adverse events
Overall safety profile	Worse	Better than 150 mg	More favorable

Table 2. Comparison of analgesic efficacy and safety outcomes for IV tramadol (150 mg), IV tramadol (100 mg), and IV ketoprofen (50 and 100 mg) in a randomized placebo-controlled study in postsurgical pain.

Tramadol was introduced in 1977 (oral) and in 1991 (IV/IM). It was not a controlled substance (CS), leading to worldwide adoption. Abuse liability and seizure risks have since emerged. It is now a CS in the U.S., UK, China, Japan, some EU, Latin American and Middle Eastern countries. It is not a CS in India, and in some African and Latin American countries. IV/IM tramadol is now available in more than 135 countries. IV tramadol is widely used for postsurgical pain management. It is not approved in the U.S. or Canada. Both study participants received a 150 mg IV dose over 2 minutes. Although this dose has previously been evaluated, the U.K. and EU SmPC (prescribing information) recommends an initial 100 mg IV bolus, followed by 50 mg every 10–20 min PRN during the first hour (maximum 250 mg), then 50–100 mg Q4–6h, not to exceed 400 mg (previously 600 mg) per day.

Summary

Key Clinical Message

- Rapid-onset seizures within minutes of dosing
- Efficacy of IV tramadol 150 mg ≈ 100 mg
- IV ketoprofen 50-100 mg 2x >> analgesia vs. tramadol
- Lower tramadol doses
- Multimodal analgesia may improve safety.

Clinical Recommendations

- Avoid high-dose IV bolus (100 or 150 mg) tramadol
- Smaller 25–50 mg incremental bolus doses
- Short infusions should reduce Cmax and seizure risk
- Consider multimodal analgesia (e.g., with NSAIDs)

Take-Home Points

- Seizures occurred within 3–4 minutes of IV tramadol
- 2/22 participants (9%) experienced seizures at 150 mg
- No seizures observed with 100 mg IV tramadol
- Low “real-world” safety margin (tramadol 100-150 mg)

Limitations

1. Case report with only two patients
2. Limited ability to determine causality
3. No EEG, neuroimaging or other diagnostic workup performed after seizures

Conclusion

Rapid-onset generalized tonic–clonic seizures occurred shortly after IV tramadol 150 mg in two patients without known seizure risk factors. These findings raise important safety concerns regarding high-dose IV tramadol for postsurgical pain. Lower dosing strategies and multimodal analgesia may provide safer pain management.

References

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