Establishing the Evidence-Based Dose for Ketorolac

East Carolina University Health Medical Centre
Department of Internal Medicine

Lasha-Giorgi Esebua, MD; Stanley Oghoghorie, MD; Mariam Dvalishvili, MD; Rana Mohamed, MD; Edward Lawson Cate, MD

2023
Our Team

Greeshma Sheri, MD
Internal Medicine
Clinical Assistant Professor

Stanley Oghoghorie
Internal Medicine
Postgraduate Year 2

Mariam Dvalishvili
Internal Medicine
Postgraduate Year 2

Rana Mohamed
Internal Medicine
Postgraduate Year 2

Edward Lawson Cate
Internal Medicine
Postgraduate Year 2

Lasha-Giorgi Esebua
Internal Medicine
Postgraduate Year 5
FDA

Premarketing clinical investigations demonstrated that 30-90 mg of ketorolac provided post-operative analgesia similar to 6-12 mg of morphine and 50-100 mg of meperidine

Ketorolac, the only parenteral NSAID available in the United States, is frequently used in the perioperative setting.
Adverse events

Reports of deaths related to Ketorolac Drug’s license get suspended in Germany and France manufacturer recommended reducing the dose of ketorolac from 150 to 120 mg per day

1996

Decreasing maximum dose

The European Committee for Proprietary Medicinal Products recommended a further maximal daily dose reduction to 60 mg

2000

Analgesic ceiling effect

Ketorolac, like other NSAIDs, exhibits an analgesic ceiling effect at 10-15 mg IV

1991-2017s

Prospective trials on pharmacodynamics of Ketorolac
Implementing Evidence-based medicine in clinical practice

2000-Present

Establishing analgesic dose

Three modern RCTs supporting the previously established analgesics ceiling

Present
### Table 2. Summary of Efficacy Measures

<table>
<thead>
<tr>
<th></th>
<th>Morphine 2 mg (n=29)</th>
<th>Morphine 4 mg (n=29)</th>
<th>Ketorolac 10 mg (n=30)</th>
<th>Ketorolac 30 mg (n=32)</th>
<th>Treatment Effect (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-hr SPID</td>
<td>0.9</td>
<td>1.8</td>
<td>2.0</td>
<td>2.6</td>
<td>0.022</td>
</tr>
<tr>
<td>6-hr SPID</td>
<td>1.4</td>
<td>3.6</td>
<td>4.3</td>
<td>5.4</td>
<td>0.004</td>
</tr>
<tr>
<td>3-hr TOTPAR</td>
<td>2.0</td>
<td>3.5</td>
<td>3.9</td>
<td>4.6</td>
<td>0.004</td>
</tr>
<tr>
<td>6-hr TOTPAR</td>
<td>3.4</td>
<td>7.2</td>
<td>7.9</td>
<td>9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to first positive PID (hrs)</td>
<td>0.5</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.826</td>
</tr>
<tr>
<td>Time to peak PID (hrs)</td>
<td>3.0</td>
<td>2.3</td>
<td>1.9</td>
<td>2.2</td>
<td>0.594</td>
</tr>
<tr>
<td>Peak PID</td>
<td>0.6</td>
<td>1.0</td>
<td>1.2</td>
<td>1.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Time to remedication (hrs)</td>
<td>1.7</td>
<td>3.3</td>
<td>4.5</td>
<td>5.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Percentage withdrawing because of inadequate pain relief</td>
<td>93.1</td>
<td>62.1</td>
<td>60.0</td>
<td>43.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall rating</td>
<td>2.0</td>
<td>2.5</td>
<td>2.6</td>
<td>2.8</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Values not sharing a common underline are statistically significantly different. See text for definition of terms.

### Summary

There were no statistically significant differences among the two ketorolac doses.

---

**Post-op pain**

**Double-blind RCT**

**Ketorolac 10 mg vs 30 mg**

- Post-operative pain
- 120 patients
- Both groups had similar score at three and six hour for
  - Summed pain intensity difference
  - Total pain relief
  - Time to first positive PID
  - Time to peak PID

---

Post-op morphine PCA use

Ketorolac 15 mg vs 30 mg

- Post-operative pain
- 70 patients
- Both groups had similar morphine consumption
- Pain scores were similar between both groups
- Both groups had similar sedation scores throughout the study period

No Difference

15 mg and 30 mg ketorolac groups showed similar results in terms of morphine consumption, pain scores, and sedation scores.

Emergency Department

Mixed ED population

- 240 patients
- Ketorolac has similar analgesic efficacy at intravenous doses of 10, 15, and 30 mg
- IV ketorolac administered at the analgesic ceiling dose (10 mg) provided effective pain relief to ED patients

Ketorolac 10 mg vs 15 mg vs 30 mg
- No difference in terms of analgesic effect for 10, 15, and 30 mg groups

Renal colic in the ED

### Table 2
Comparison of the pain intensity as defined by VAS between the study groups within the first 60 minutes after the intervention

<table>
<thead>
<tr>
<th>VAS score</th>
<th>Group A (10 mg)</th>
<th>Group B (20 mg)</th>
<th>Group C (30 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>90 (85–92)</td>
<td>80 (73–90)</td>
<td>90 (83–90)</td>
</tr>
<tr>
<td>After 15 min</td>
<td>61 (58–70)</td>
<td>60 (50–68)</td>
<td>60 (60–70)</td>
</tr>
<tr>
<td>After 30 min</td>
<td>40 (35–50)</td>
<td>40 (40–49)</td>
<td>40 (34–50)</td>
</tr>
<tr>
<td>After 45 min</td>
<td>15 (10–20)</td>
<td>20 (13–25)</td>
<td>13 (10–18)</td>
</tr>
<tr>
<td>After 60 min</td>
<td>5 (0–10)</td>
<td>5 (0–10)</td>
<td>5 (0–10)</td>
</tr>
</tbody>
</table>

Note: Data are reported as median (95% CI).
Abbreviation: VAS, visual analog scale.

### Summary
Consectetur met adipiscing elit. Aenean ac elit a felis

---

**Ketorolac 10 mg 15 mg vs 30 mg**

- 165 patients
- 10 mg was not inferior to 15 and 30 mg administered intravenously
- Rescue analgesic administration was similar between the groups

---

**Eidinejad L, et al Acad Emerg Med. 2021**
MSK pain in the ED

**Single-blinded RCT**

**Ketorolac 15 mg vs 60 mg**
- 110 patients
- Noninferiority study
- Acute musculoskeletal pain in the emergency department
- 15 mg was not inferior to 15 and 30 mg administered intravenously

**Summary**
15 mg is non-inferior to 60 mg for acute MSK pain in adults presenting to the ED

Ketorolac use

ECU Health Medical Center

Ketorolac 60 mg
IM or IV administration of Ketorolac in the ED from 08/01/2022 to 12/1/2022

Ketorolac 30 mg
IM or IV administration of Ketorolac in the ED from 08/01/2022 to 12/1/2022

Ketorolac 15 mg
IM or IV administration of Ketorolac in the ED from 08/01/2022 to 12/1/2022
Inappropriate ketorolac dose use

Why are we doing this project?
Inappropriate ketorolac dose use

What is the problem we are addressing?
Inappropriately high ketorolac dose use

Who is affected?

Why does it matter?
How does it affect the patient? Patient safety, outcomes, cost of care (direct and indirect)

Institute of Medicine’s six dimensions of quality

What are the next steps
System wide adoption, direct patient outcome and cost of care measurement
Model of Improvement

Act
Adjusting QI project

Plan
Establishing intervention
Establishing Measures

Study
Gathering and analyzing data

Do
Implementing interventions
Choosing the target

Current selectable Ketorolac doses in EPIC are 15 mg, 30 mg and 60 mg as shown in the attached image. These preset doses likely contribute to the increased ordering and administration of >15 mg ketorolac.

Changing the environment

Eliminating 30 mg and 60 mg buttons entirely which will lead to manual input of these doses if desired.

Decision support

If higher dose is entered, a red message will appear suggesting 15 mg of ketorolac be ordered as opposed to 30/60.
Model of Improvement

**Act**
- Adjusting QI project

**Plan**
- Establishing intervention
- Establishing Measures

**Do**
- Implementing interventions

**Study**
- Gathering and analyzing data

**A**

**P**

**S**

**D**


