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Ketorolac Ceiling Dose Implementation in the Emergency Department

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The speaker and mentors have no actual or potential conflict of interest in relation to this presentation.

Background: Ceiling Effect with NSAIDs

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to have a "ceiling dose“
  - Most effective dose for treatment
- Above the ceiling dose:
  - No further pain relief
  - More adverse effects

Motov. *Ann Emerg Med*. 2017 Aug;70(2):177-84.

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Background: Ketorolac

Class:

- NSAID
- Reversible binding
- Nonselective COX-1 and COX-2 inhibitor

Indications for use:

- Approved: acute pain, short-term pain relief
- Off-label: migraine, severe acute pain

Administration:

- Oral (PO)
- ***Intramuscular (IM)***
- ***Intravenous (IV)***

Product Information: Ketorolac Tromethamine Injection. Hospira, Inc (per manufacturer), Lake Forest, IL 60045, 2020.

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Background: Ketorolac Dosing

Weight ≥50 kg and <65 years of age:

- **IV:** 30 mg as a single dose or 15 to 30 mg every 6 hours as needed; maximum daily dose: 120 mg/day
- **IM:** 30 to 60 mg as a single dose or 15 to 30 mg every 6 hours as needed; alternatively, may administer 10 to 30 mg every 4 to 6 hours as needed

Weight <50 kg or ≥65 years of age:

- **IV:** 15 mg as a single dose or 15 mg every 6 hours as needed; maximum daily dose: 60 mg/day
- **IM:** 30 mg as a single dose or 15 mg every 6 hours as needed; alternatively, may administer 10 mg every 4 to 6 hours as needed

Renal Dose Adjustments:

- eGFR 10 to 50 mL/minute/1.73 m^2
  - Some experts recommend avoiding use
  - Consider 7.5 to 15 mg every 6 hours

Product Information: Ketorolac Tromethamine Injection. Hospira, Inc (per manufacturer), Lake Forest, IL 60045, 2020.

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Background: Concerns with Use

- Appropriate use– short term **(up to 5 days)** for the management of moderately severe acute pain that requires analgesia at the opioid level
- Box Warnings for NSAIDs:
  - Cardiovascular thrombotic events
  - Gastrointestinal (GI) risk– causes peptic ulcers, GI bleeding, and/or perforation of stomach or intestines
  - Renal risk– Contraindicated in advanced renal impairment and in patients at risk for renal failure due to volume depletion, acute kidney injury

Product Information: Ketorolac Tromethamine Injection. Hospira, Inc (per manufacturer), Lake Forest, IL 60045, 2020.

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SUPPORTING LITERATURE

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Motov et al.

Motov et al. Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial		
Study Design	Randomized, double-blind study conducted at a 711-bed urban community teaching hospital	
Inclusion/Exclusion	Adults 18 to 65 years old Acute pain (intensity 5) Routinely be treated with ketorolac	Active peptic ulcer disease, acute GI hemorrhage, history of renal/hepatic insufficiency Allergy to NSAID Unstable vital signs Previous analgesic medication received
Outcomes	Primary: Reduction in pain score at 30 minutes from medication administration	Secondary: Rates and percentages of subjects experiencing adverse effects and requiring rescue analgesia
Interventions	Ketorolac 10, 15, 30 mg IV	

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Motov. *Ann Emerg Med*. 2017 Aug;70(2):177-84.

Motov et al.

Motov et al. Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial

Baseline Characteristics	240 total patients– 80 assigned to each group (10, 15, 30 mg IV ketorolac) Mean ages 41.5, 40.1, and 38.8 years old % Male 39, 32, 37
Results	

Pain Scores at 30 Minutes	10 mg (N=80)	15 mg (N=80)	30 mg (N=80)
Baseline, mean	7.7	7.5	7.8
30 minutes post administration, mean	5.2	5.1	4.8

- There was no difference in pain score reduction from baseline to 30 minutes across the 3 dose groups

There was no difference in rates of rescue medication use (morphine) across the 3 treatment groups

- At 30-minute follow-up, 5%, 3.8%, and 5% of patients in the 10, 15, and 30 mg group received rescue medication

Safety: There was no difference in rates of adverse events reported (nausea, dizziness, headache)

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Motov. *Ann Emerg Med*. 2017 Aug;70(2):177-84.

Soleyman-Zomalan et al.

<table>
<tr><th colspan="2">Soleyman-Zomalan et al. Patterns of Ketorolac Dosing by Emergency Physicians</th></tr>
<tr><td>Study Design</td><td>Single center retrospective, descriptive study</td></tr>
<tr><td>Purpose</td><td>Characterize patterns of ketorolac administration in ED patients at an urban New York City community teaching hospital from 2003 to 2013</td></tr>
<tr><td>Results</td><td>49,606 ketorolac administration given to 34,026 patients
<table>
<tr><th></th><th>IV</th><th>IM</th></tr>
<tr><td>Total administrations</td><td>38,688</td><td>9,916</td></tr>
<tr><td>Dosing
10 mg
15 mg
30 mg
60 mg</td><td>
203 (0.5%)
5,288 (13.67%)
32,715 (84.56%)
15 (0.03%)</td><td>
361 (3.7%)
102 (1.02%)
4,916 (49.57%)
4,553 (45.92%)</td></tr>
</table>
Most common diagnoses at discharge were renal colic (21%), low back pain (17%), and abdominal pain (11%)</td></tr>
<tr><td>Key Points</td><td>Ketorolac was prescribed above ceiling dose in 97% of patients who received IV route and in 96% of patients who received IM route</td></tr>
</table>

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Self-Assessment Question #1

Ketorolac is a/an _____ COX _____ inhibitor

A. Reversible, COX-2 selective

B. Irreversible, COX-2 selective

C. Irreversible, COX-1 and -2 nonselective

D. Reversible, COX-1 and -2 nonselective

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Self-Assessment Question #2

The duration of ketorolac use should be limited to how many days due to risk of adverse events:

A. 3 days

B. 5 days

C. 7 days

D. 10 days

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Purpose

To evaluate change in pain scores after implementing a ketorolac ceiling dose for both IV and IM doses compared to previous standard dosing in the emergency department (ED).

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Setting

- Parkview Health
  - Not-for-profit, community-owned organization
  - Northeast Indiana and northwest Ohio
  - 10 hospital health system
- Emergency departments
  - Parkview Regional Medical Center (PRMC)
  - Parkview Hospital Randallia (PVH)

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Ordering at PRMC and PVH ED

Doses ranging from 10 to 60 mg

Both IV and IM routinely used

- IV use is more common than IM
- Higher 60 mg dose more common with IM administration

30 mg dose was ordered most often

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Intervention

- Ketorolac ceiling dose of 15 mg for intravenous and intramuscular routes
  - Provided written education to ED staff
  - Removed personal order preferences for ketorolac
  - Established high dose warning and soft stop for ketorolac orders > 15 mg

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Design

- Retrospective study
- Multicenter
  - Ceiling dose established at all Parkview locations
  - Only evaluating PRMC and PVH

Pre-Implementation	Post-Implementation
Usual/Standard ED dosing practices	Ketorolac 15 mg ceiling dose
July 1, 2021-October 26, 2021	October 27, 2021-January 31, 2022

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Design

Inclusion Criteria

- Adults ≥ 18 years old presenting to the emergency department
- Acute pain
- Received ketorolac IV/IM

Exclusion Criteria

- Received analgesic medication in the ED prior to ketorolac
- Missing pain scores

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Endpoints

- Primary
  - Evaluate change in pain scores after receiving ketorolac pre-implementation and post-implementation
- Secondary
  - Rescue medication use
  - Admission vs discharge
    - Medication prescribed at discharge from ED
    - Initial inpatient medications ordered for pain
    - Change in serum creatinine for admitted patients

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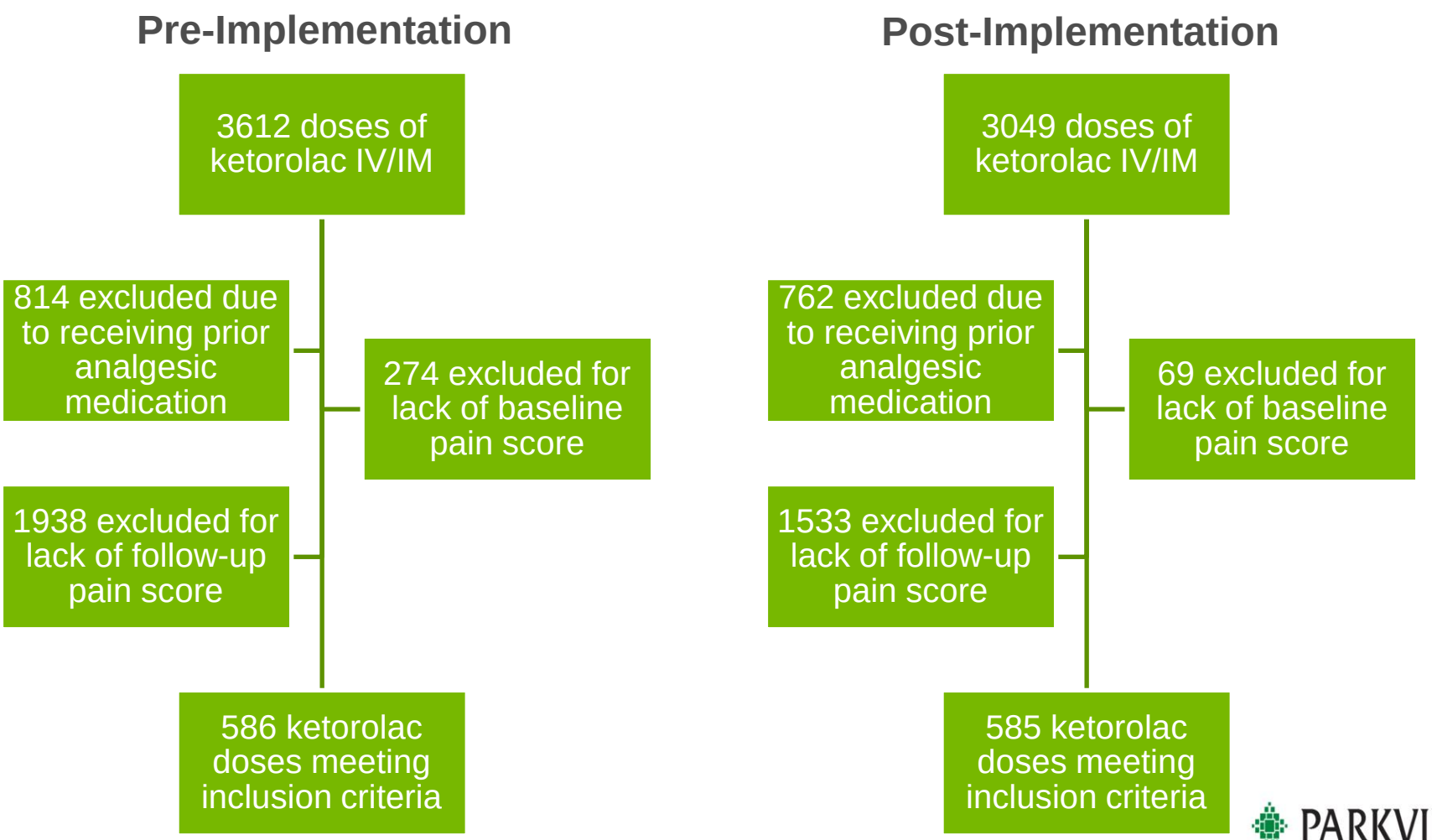
Patient Inclusion



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Baseline Characteristics

	Pre-Implementation (N=586)	Post-Implementation (N=585)
Age, yrs, median (range)	39 (18-86)	37 (18-85)
Female sex, no. (%)	375 (64)	390 (66.6)
Weight, kg, median (range)	84.8 (35.4-245.8)	85.3 (43.1-256.3)
Baseline Creatinine, mg/dL, median (range)	0.80 (0.44-2.22)	0.80 (0.41-2.01)
Ketorolac doses, no. (%) • 15 mg • 30 mg • 60 mg	 194 (33.1) 351 (59.9) 41 (7)	 **433 (74)** 145 (24.8) 7 (1.2)
Intravenous, no. (%) Intramuscular, no. (%)	447 (76.3) 139 (23.7)	430 (73.5) 155 (26.5)

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Baseline Characteristics

	Pre-Implementation (N=586)	Post-Implementation (N=585)
Past Medical History, no. (%)		
• Cardiac Condition	85 (14.5)	72 (12.3)
• Chronic Pain	15 (2.5)	3 (0.5)
• Chronic Kidney Disease (CKD)	4 (0.7)	8 (1.4)
Prior to Admission Medications, no. (%)		
• ACE-I	42 (7.2)	35 (6.0)
• ARB	30 (5.1)	39 (6.7)
• Diuretic	64 (10.9)	57 (9.7)
• NSAID	83 (14.2)	199 (34)
• Opioid	38 (6.5)	154 (26.3)
• Acetaminophen	11 (1.9)	31 (5.3)

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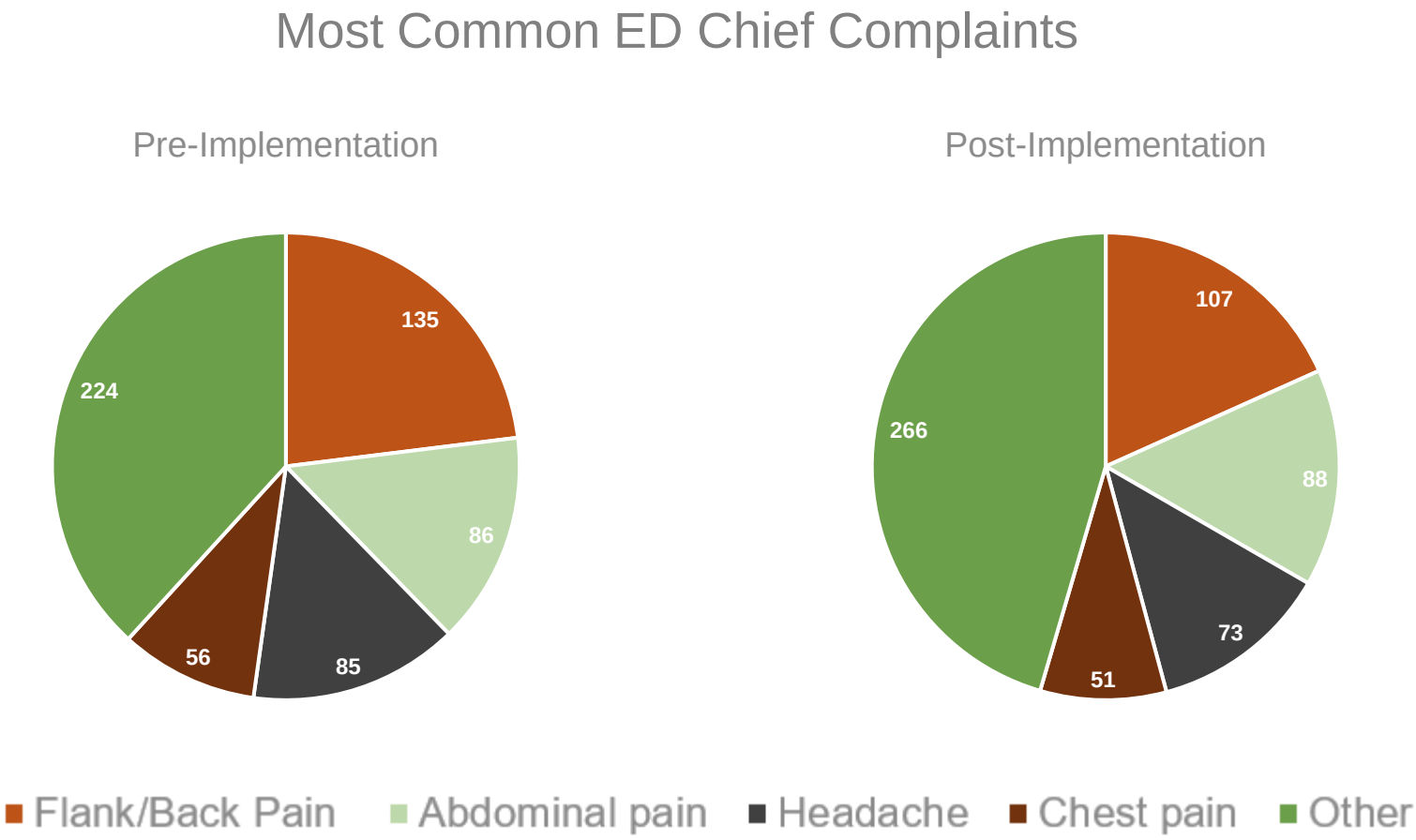
Baseline Characteristics



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Results– Primary Endpoint

	Pre-Implementation (N=586)	Post-Implementation (N=585)
Baseline Pain Score, Median (range)	8 (0-10)	8 (0-10)
Post-Ketorolac Pain Score, Median (range)	5 (0-10)	5 (0-10)
Change in Pain Score	3	3
Ketorolac Dose, no. (%) • 15 mg • 30 mg • 60 mg	 194 (33.1) 351 (59.9) 41 (7)	 433 (74) 145 (24.8) 7 (1.2)

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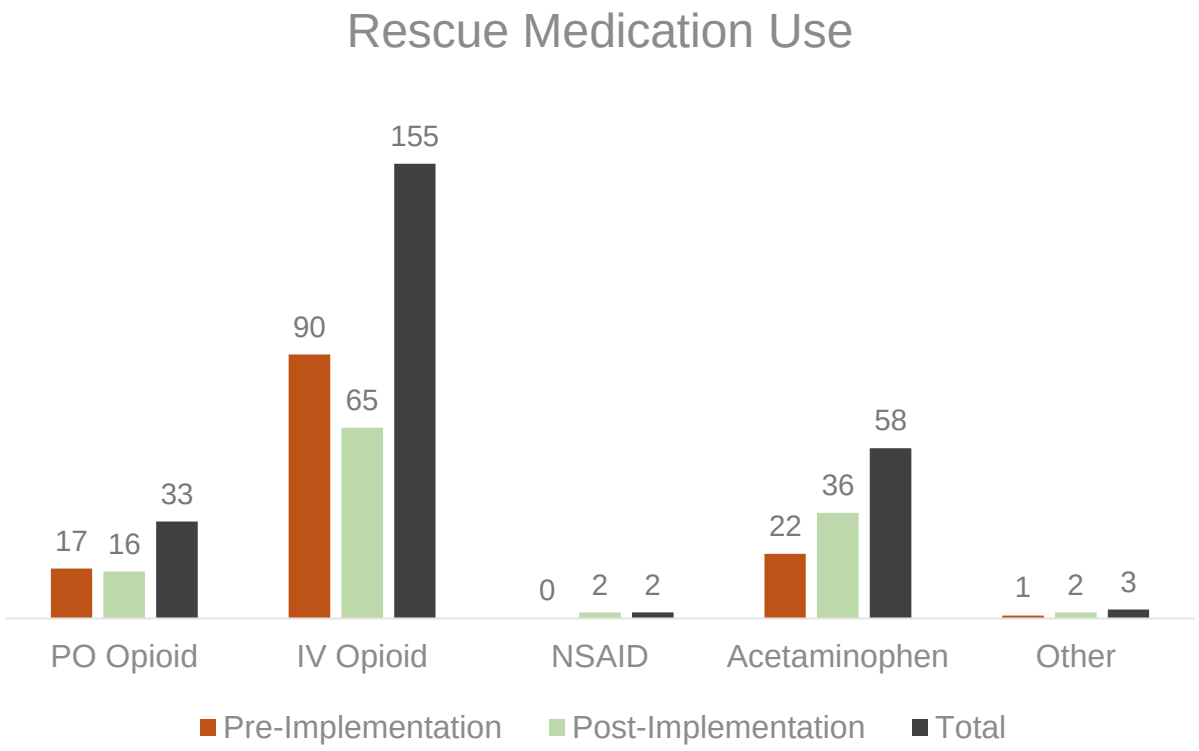
Results– Secondary Endpoint

	Pre-Implementation (N=586)	Post-Implementation (N=585)
Required Rescue Medication, no. (%)	130 (22.8)	121 (20.7)



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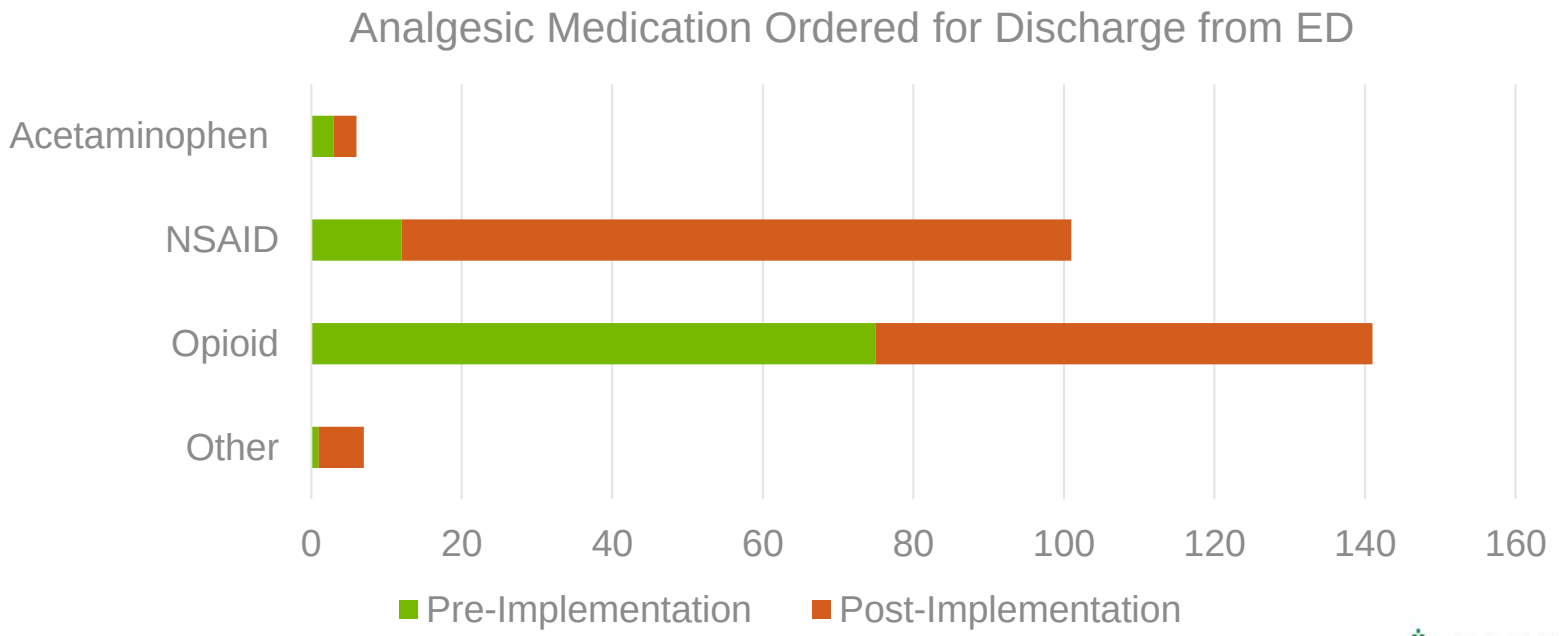
Results– Secondary Endpoint

	Pre-Implementation (N=586)	Post-Implementation (N=585)
Discharged from ED, no. (%)	535 (91.3)	523 (89.4)
Discharged with Analgesic Medication, no. (%)	87 (16.3)	145 (27.7)



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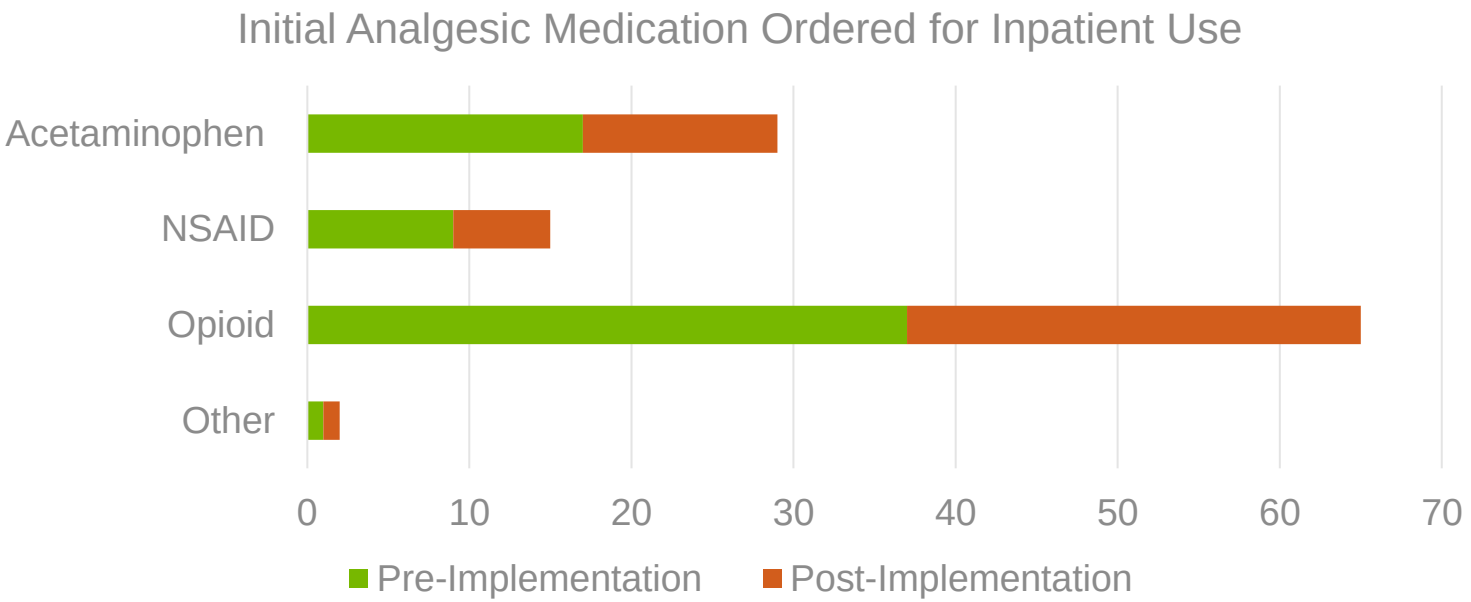
Results– Secondary Endpoint

	Pre-Implementation (N=586)	Post-Implementation (N=585)
Admitted, no. (%)	51 (8.7)	65 (10.6)
Patients with Analgesic Medication Ordered, no. (%)	35 (68.6)	30 (46.2)



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Results– Secondary Endpoint

	Pre-Implementation (N=16)	Post-Implementation (N=19)
Serum Creatinine, baseline (mg/dL), median (range)	0.95 (0.48-1.63)	0.81 (0.6-1.41)
Serum Creatinine, Day 2 of Admission (mg/dL), median (range)	0.89 (0.42-3.61)	0.72 (0.44-1.24)
Change in Serum Creatinine (mg/dL)	-0.06	-0.09

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Conclusion and Future Direction

- One-time doses of IV/IM ketorolac 15 mg provided similar results for:
  - Pain relief
  - Need for rescue medication
- Post-implementation included more post-dose pain scores
- No conclusion regarding safety can be drawn
- Future direction
  - Expanding the ceiling dose system wide

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References

- Product Information: Ketorolac Tromethamine Injection. Hospira, Inc (per manufacturer), Lake Forest, IL 60045, 2020.
- Eidinejad L, Bahreini M, Ahmadi A, et al. Comparison of intravenous ketorolac at three doses for treating renal colic in the emergency department: a noninferiority randomized controlled trial. Acad Emerg Med. 2021;00:1-8.
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- Soleyman-Zomalan E, Motov S, Likourezos A, et al. Patterns of ketorolac dosing by emergency physicians. World J Emerg Med. 2017;8(1):43-6.

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