Poster# 45

Post-operative Vomiting With IV Oliceridine in Post-operative Recovery: a Single-group Prospective Cohort Study

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BACKGROUND

- Post-operative (post-op) vomiting is common during post-op recovery and can compromise quality of care, delay discharge, and resumption of daily activities
- Oliceridine is a μ-opioid receptor agonist indicated for use in adults for the management of acute pain severe enough to require an intravenous (IV) opioid analgesic and for whom alternative treatments are inadequate
- Oliceridine engages the G-protein-coupled receptor signaling pathway, with limited recruitment of the β-arrestin pathway that is thought to mediate opioid-related adverse events including gastro-intestinal (GI) complications
- Exploratory analysis from Phase 3 trials of IV oliceridine suggested improved complete GI response (no vomitting and no rescue antiemetics) compared to IV morphine
- We therefore prospectively evaluated complete GI response in patients given IV oliceridine during and after major noncardiac surgery

METHODS

Study Design

- VOLITION was an open-label, single-arm, multi-center, real-world outcomes study that assessed the effectiveness of IV oliceridine on a broad range of clinical outcomes seen during the post-operative recovery period following use of IV opioid medications for acute pain management
- Among outcomes measured were gastrointestinal (GI) tolerability, respiratory compromise, and risk of delirium
- Enrolled patients were scheduled to undergo a major, noncardiac surgical procedure
- The study was conducted at 3 locations: Cleveland Clinic – Main Hospital (CC Main) and Fairview Campuses (CC Fairview); Wake Forest Baptist Health Medical Center (WFBH)

Treatment

- IV oliceridine was given as a 1.5-mg loading dose at surgical closure, followed by 0.35-0.5 mg of IV oliceridine via a patient-controlled analgesia (PCA) device, with a 6-minute lockout period; additional boluses of 1-3 mg q 1-3 hours were provided thereafter as needed
- All other clinical care, including use of standard pre-operative antiemetic medication or use of supplemental IV opioids, was determined by the treating clinical staff consistent with hospital routine and in accordance with local ERAS protocols

Outcome Assessments

Gastrointestinal	• Adverse event (AE) reports of nausea and vomiting and use of post-operative rescue antiemetics were used to identify the presence of a 'complete GI response', defined as having no post-operative vomiting AND no rescue antiemetic use • The incidence of post-operative ileus was also obtained in the AE record
Respiratory	• Continuous respiratory monitoring was obtained (data collection blinded to clinical staff) using the Masimo Radius VSM device • SpO_2, end-tidal CO_2, respiratory rate, heart rate
Cognitive Status	• Delirium risk was estimated by using the 3D-CAM bedside monitoring screening method • Sedation and agitation were measured using the Pasero Opioid-induced Sedation Scale (POSS) and the Richmond Agitation-Sedation Scale (RASS)

- This presentation focuses on a detailed description of the GI outcomes; the primary outcomes in the respiratory and cognitive domains are also summarized

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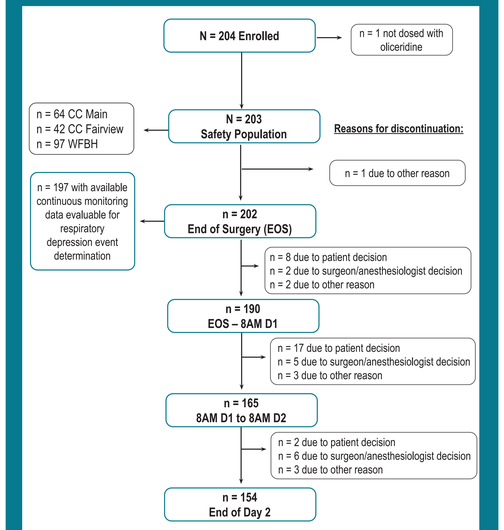
RESULTS

Study Population

Figure 1. Study Population: Disposition



- **Figure 1** shows the disposition of patients included in the study
- Major demographic and clinical characteristics of the study population are shown in **Table 1**

Table 1. Study Population: Demographic and Clinical Features

Clinical Characteristic	Results (N = 203)
Age: mean (SD); range	57.1 (16.14); 19, 89
Sex: Male	106 (52.2%)
BMI (kg/m²): mean (SD); range	28.72 (6.55); 14.0, 50.3
ASA Status	
I	3 (1.5%)
II	64 (31.5%)
III	128 (63.1%)
IV	8 (3.9%)
Type of Surgery	
Abdominal	175 (86.2%)
Other	28 (13.8%)
Surgery Duration (hrs): mean (SD); range	4.8 (2.1); 1.2, 12.6
Apfel Score	
1	9 (4.4%)
2	90 (44.3%)
3	85 (41.9%)
4	19 (9.4%)
PRODIGY Risk Score: mean (SD); range	12.5 (8.3); 0, 34
STOP-BANG Score	
Low Risk (<=2)	89 (43.8%)
Intermediate Risk (3 to <5)	74 (36.5%)
High Risk (>=5)	30 (14.8%)

Gastrointestinal

- GI outcomes are presented in Table 2
- GI-related adverse events are summarized in Table 3
- Overall, 115 GI patients received received additional antiemetic medications including ondansetron (n = 80), prochloperazine (n = 20), scopolamine (n = 7), metoclopramide (n = 3), droperidol (n = 2), promethazine (n = 2), and dexamethasone (n =1)

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*Table 2. Summary of Complete GI Response**

	CC Main (n = 64)	CC Fairview (n = 42)	WFBH (n = 97)	Total (N = 203)
Overall Complete GI Response	31 (48.4%)	23 (54.8%)	53 (54.6%)	107 (52.7%)
Complete GI Response by Subgroup				
Subjects Who Received Oliceridine Only (n = 129)	19 (61.3%)	16 (69.6%)	43 (81.1%)	78 (72.9%)
Subjects Who Received Oliceridine Plus At Least One Additional IV Opioid (n = 74)	12 (38.7%)	7 (30.4%)	10 (18.9%)	29 (27.1%)

*Complete GI Response = No vomiting and no rescue antiemetic use during the entire post-operative period

- Overall, 107 patients (52.7%) were categorized as having a 'complete GI response' during the post-operative study period. Among those patients treated only with IV oliceridine, the incidence of 'complete GI response' was seen among 78 patients, which represented 72.9% of the total complete responder population.
- Among the study population, there were 10 patients (4.9%) with an AE of ileus, however, in only 1 patient was this determined by the clinician to be due to the use of study drug.

Table 3. Postoperative GI Adverse Event Summary (N=203)

System Organ Class Preferred Term	n (%) [# of Events]
SAE GI disorders	5 (2.5%)[5]
Functional gastrointestinal disorder	1 (0.5%)[1]
Gastrointestinal ulcer haemorrhage	1 (0.5%)[1]
Proctalgia	1 (0.5%)[1]
Small intestinal obstruction	2 (1.0%)[2]
SAE Injury, poisoning and procedural complications	13 (6.4%) [13]
Intestinal anastomosis complication	1 (0.5%) [1]
Postoperative ileus	9 (4.4%) [9]
AE GI disorders	12 (5.9%)[18]
Nausea	9 (4.4%)[9]
Pneumoperitoneum	1 (0.5%)[1]
Vomiting	8 (3.9%)[8]
AE Injury, poisoning and procedural complications	4 (2.0%) [5]
Postoperative ileus	2 (1.0%) [3]

- Overall, there were 36 SAEs among 31 patients*
  - None were related to study drug administration in the opinion of the study physician
  - All potentially-related AEs reported were consistent with the product label

*(data not shown)

Respiratory

- Respiratory compromise, as measured by the continuous respiratory monitoring record, was reviewed by an external panel to determine clinical validity of any of the following criteria appearing in the monitoring record (NOTE: the criteria chosen were modeled after the criteria used in the recently reported PRODIGY study):
  - end-tidal $PCO_2 \leq 15$ mmHg for ≥3 minutes
  - respiratory rate ≤ 5 breaths/minute for ≥3 minutes
  - $SpO_2 \leq 85\%$ for ≥3 minutes
  - apnea episode lasting >30 seconds
- Any patient who met adjudicated criteria of one or more of these outcomes was counted as having clinically meaningful respiratory compromise

Table 4. Summary of Incidence of Adjudicated Respiratory Compromise

Hospital Site	Study Population n	Primary Aim* n (%) [# events]
CC Main	63	14 (22.2%) [39]
CC Fairview	41	11 (26.8%) [60]
WFBH	93	20 (21.5%) [76]

NOTE: *A patient met primary aim if they had 1 or more respiratory events; e.g., a patient having 2 events occurring at the same time was counted as meeting the primary aim criterion once

In the study population, **45 patients (22.8% of the evaluable study population with continuous monitoring available)** met the primary aim criterion outcome of experiencing an episode of respiratory compromise

Cognitive Status

- In the overall study population, 8 patients (3.9%) met criteria on the 3D-CAM for a potential diagnosis of delirium
- Overall, 92.9% - 96.6% of patients were observed on the RASS to report feeling "alert and calm" at every observation point during the post-operative study period
- Using the POSS, a majority of patients (65.5%) were assessed as being "awake and alert" on the evening of the 1st post-op day, and 88.4% - 93.6% of patients were rated at this level on the 1st and 2nd full post-op study days

CONCLUSIONS

- Patients treated with IV oliceridine had favorable clinical outcomes as measured by indices of GI tolerability, respiratory compromise, cognitive dysfunction, sedation and agitation, when used in a medically complex surgical population, and used in accordance with the prescribing information
- These outcomes compare favorably to published historical benchmarks using similar outcome measures in a comparable patient population
  - 107 of 203 (52.7%) patients met criteria for complete GI response (no post-op antiemetic use, no post-op vomiting)
    - ◊ Complete responder outcome among patients in pooled Apollo Phase 3 RCTs = 46.2%, 39.7% for 0.35 mg and 0.5 mg PCA demand doses, respectively. Complete responder outcome for 1.0 mg morphine PCA = 30.8%
    - ◊ As reflected in the OLINVYK® label, nausea and vomiting were two of the most common adverse events reported in the controlled clinical trials
  - 10 of 203 (4.9%) patients experienced post-operative ileus, only 1 event was considered to be drug-related
  - 8 of 203 (3.9%) patients met 3D-CAM screening criteria for a likely presence of delirium
    - ◊ More than 90% of patients assessed with the RASS reported feeling "alert and calm" at all post-operative time points
    - ◊ From the first POD onward, a majority of patients were assessed as being "awake and alert" on the POSS (65.5% on the evening of POD 0, 88.4-93.6% on POD 1 and 2)
    - ◊ Sedation is an established risk of opioids, including OLINVYK®
  - 45 of 197 (22.8%) patients met the primary outcome criteria for respiratory compromise
    - ◊ Historical benchmark comparison: PRODIGY study reported an incidence ranging from 46% - 62% using similar methodology, primary outcome definition, and patient study population
    - ◊ As with all opioids, serious, life-threatening, or fatal respiratory depression may occur in patients treated with OLINVYK®, as indicated in the boxed warning