Gastrointestinal Adverse Effects Associated with the Use of Intravenous Oliceridine Compared to Intravenous Hydromorphone or Fentanyl in Acute Pain Management Utilizing Indirect Treatment Comparison Methods

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Background

- Indirect treatment comparisons (ITCs) are used to compare treatments when there is no or insufficient evidence from head-to-head clinical trials.[1]
- ITCs compare effects of treatments vs. a common comparator, often placebo.[1]
- Unbiased ITCs require homogeneity, study similarity, and consistency of evidence.[1]
- Treatment for post-operative acute pain management commonly includes opioids (e.g., morphine, hydromorphone, fentanyl), which have adverse effects (AEs) such as nausea and vomiting.[2] In late 2020, oliceridine was approved for use in the treatment of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.
- The effects and AEs of oliceridine, fentanyl, and hydromorphone have been directly compared to morphine in clinical trials.
- No clinical trials have directly compared oliceridine to fentanyl or hydromorphone.

Objectives

- Identify potential opioid comparators and AEs of interest.
- Conduct an ITC between oliceridine vs. morphine clinical trials and studies evaluating fentanyl and/or hydromorphone vs. morphine.

Methods

Literature Search

- PubMed literature searches: papers in English, 1995-2022, US and Canada, comparing oliceridine vs. morphine and morphine vs. fentanyl or hydromorphone.
- Because data for opioid-induced respiratory depression (OIRD) was extremely limited, nausea and/or vomiting was selected as the AE of interest for the ITC.

Adjusted ITC Analysis

- Pooled data for oliceridine were obtained from two Phase 3 randomized placebo and active controlled trials [(APOLLO-1 (orthopedic surgery)][3] and [APOLLO-1 (plastic surgery)][4]). Patients received demand doses of oliceridine (0.35mg or 0.5mg) or morphine (1.0mg).
- Morphine-equivalent dosing used in the clinical trials in the ITC were similar.
- Aggregate data for hydromorphone vs. morphine were obtained from two randomized, double-blind clinical trials.[5,6]
- Aggregate data for fentanyl vs. morphine were obtained from a retrospective study[7] and a prospective randomized study.[8]
- Baseline population demographics and clinical characteristics were compared.
- A Bucher Anchor-Based Indirect Comparison[9] was used. This approach partially maintains the strength of randomization and can be applied with minimal information regarding the common comparator.
- Because complete GI response was not reported in the hydromorphone and fentanyl studies, achievers of complete GI response in the oliceridine group were compared to no antiemetic use in the hydromorphone and fentanyl groups.
- The difference in risk differences (RD) for oliceridine vs. hydromorphone and oliceridine vs. fentanyl were calculated. RD can be readily translated into number needed to treat (NNT). RD = difference between the proportions of achievers of complete GI response within the populations. Difference in RD was calculated by:

Difference in RD = (Complete GI Response oliceridine − Complete GI Response morphine) − (No Antiemetic Use hydromorphone − No Antiemetic Use morphine)

Results

- In studies where oliceridine, fentanyl, and hydromorphone were compared to morphine, the only common AE was nausea and vomiting, with similar endpoints and sufficient incidence to be compared.
- Patients treated with oliceridine were less likely to develop nausea and vomiting than patients treated with hydromorphone or fentanyl.
- The NNT analysis showed oliceridine's NNT was a low number (<10) compared to fentanyl and hydromorphone.

Table 1: Baseline demographics and clinical characteristics of populations

Study and characteristics	Comparators		Morphine
Plastic Surgery (Singla 2019)[4]	Oliceridine (0.35mg), n=80	Oliceridine (0.5mg), n=80	Morphine (1.0mg), n=83
Mean age (SD)	42.0 (10.0)	40.4 (10.0)	40.4 (10.4)
Female, N (%)	80 (100.0)	80 (100.0)	81 (97.6)
Mean baseline pain score (SD)	7.4 (1.6)	7.5 (1.6	7.3 (1.5)
Pain responder rates 48h post-surgery*	76.3%	70.0%	78.3%
Orthopedic Surgery (Viscusi 2019)[3]	n=79	n=79	n=76
Mean age (SD)	43.6 (13.9)	46.9 (13.8)	43.3 (14.1)
Female, N (%)	65 (82.3)	66 (83.5)	65 (85.5)
Mean baseline pain score (SD)	6.6 (1.9)	6.5 (1.7)	6.7 (1.6)
Pain responder rates 48h post-surgery*	62.0%	65.8%	71.1%
Acute Pain in ED (Chang 2006)[5]	Hydromorphone, n=97		Morphine, n=94
Mean age	42		41
Female, N (%)	62 (54)		61 (65)
Baseline Pain Score, N (%)			
6	5 (5)		6 (6)
7	2 (2)		10 (11)
8	13 (13)		14 (15)
9	6 (6)		14 (15)
10	71 (73)		50 (53)
Pain Location, N (%)			
Abdomen/pelvis	66(68)		68 (74)
Mean Change Pain Score Baseline - 2h**	-5.4		-4.5
Elective Day Surgery (Shanthanna 2019)[6]	Hydromorphone, n=203		Morphine, n=199
Mean age (SD)	47.1 (14.0)		46.1 (13.8)
Female, N (%)	126 (62)		132 (66)
Preoperative pain in the operative area, N (%)	83 (41)		83 (42)
Type of surgery, N (%)			
Laparoscopic	185 (91)		194 (97)
Mean Pain Score 24h post-surgery (SD)**	4.3 (2.2)		4.1 (2.2)
Out-of-Hospital Analgesia (Fleischman 2010)[7]	Fentanyl, n=363		Morphine, n=355
Age, Median (95% CI)	61 (59-63)		59 (56-61)
Female, N (%)	230 (63.4)		205 (57.8)
Mean Initial Pain Scores (95% CI)	8.3 (8.1-8.5)		8.1 (7.9-8.4)
Chief Complaint, N (%)			
Extremity and hip pain and burns	244 (67)		240 (68)
Mean Decrease Pain Scores (95% CI)**	0.8 (0.4-1.1)		0.9 (0.5-1.2)
Painful Ambulatory Surgery (Claxton 1997)[8]	Fentanyl, n=29		Morphine, n=29
Mean Age (SD)	34 (10)		37 (11)
Female, N (%)	14 (48.3)		8 (27.6)
Type of Surgery, N (%)			
Arthroscopy	22 (75.9)		23 (79.3)
Pain Scores 24h post-surgery, N (%)			
Mild	4 (14)		5 (17)
Moderate	22 (76)		15 (52)
Severe	3 (10)		9 (31)

*Equi-analgesic to morphine using a noninferiority analysis

**Not statistically significant

Table 2: ITC Analysis Results

	Difference in RD (Risk Difference)	95% Confidence Interval (CI)	p-value	Number Needed to Treat (NNT)	95% CI	p-value
Oliceridine vs hydromorphone						
Orthopedic surgery vs Chang 2006[5]	23.03%	5.95%; 40.12%	.008	4.34	2.49; 16.82	.008
Plastic surgery vs Chang 2006[5]	9.98%	-6.49%; 26.45%	.235			
Combined vs Chang 2006[5]	16.55%	2.36%; 30.74%	.022	6.04	3.25; 41.84	.022
Orthopedic surgery vs Shanthanna 2019[6] (vomiting)	22.10%	8.18%; 36.03%	.002	4.52	2.77; 12.22	.002
Plastic surgery vs Shanthanna 2019[6] (vomiting)	9.05%	-4.11%; 22.21%	.178			
Combined vs Shanthanna 2019[6] (vomiting)	15.62%	5.47%; 25.77%	.003	6.40	3.88; 18.28	.003
Orthopedic surgery vs Shanthanna 2019[6] (nausea)	20.43%	5.72%; 35.14%	.006	4.89	2.85; 17.48	.006
Plastic surgery vs Shanthanna 2019[6] (nausea)	7.38%	-6.60%; 21.37%	.301			
Combined vs Shanthanna 2019[6] (nausea)	13.95%	2.75%; 25.16%	.015	7.17	3.97; 36.36	.015
Oliceridine vs fentanyl						
Orthopedic surgery vs Claxton 1997[8]	8.1%	-15.9%; 32.0%	.511			
Orthopedic surgery vs Fleischman 2010[7]	24.15%	9.97%; 38.31%	.001	4.14	2.61; 10.03	.001
Plastic surgery vs Fleischman 2010[7]	11.10%	-2.32%; 24.52%	.105			
Combined vs Fleischman 2010[7]	17.66%	7.17%; 28.16%	.001	5.66	3.55; 13.95	.001

Conclusions

- When AEs were compared in an adjusted ITC analysis using morphine as the common comparator, oliceridine was found to significantly reduce the incidence of nausea and/or vomiting or the need for antiemetics in orthopedic surgical procedures compared to hydromorphone or fentanyl. Results in plastic surgery were not significantly different.
- Given the consistent lack of difference in the incidence of nausea and vomiting between morphine and hydromorphone or fentanyl, and the two clinical trials for oliceridine vs morphine that show a difference in the incidence of nausea and vomiting favoring oliceridine, the results of the ITC analysis appear consistent with published studies.
- The NNT analysis, comparing oliceridine to both fentanyl and hydromorphone, showed a low number (<10), indicating a favorable GI tolerability profile of oliceridine versus fentanyl or hydromorphone.
- Despite their limitations, ITCs can be useful for healthcare decision makers.
  - Providers can use results to support use of oliceridine in patients at risk of nausea and vomiting.
  - Payers may consider results for reimbursement and benefit design between similar drugs in the class.
  - The NNT results may be helpful in the peri-operative setting where vomiting episodes can disrupt the healthcare team and decrease patient satisfaction.

Limitations

- Limited data availability for the ITC
- Limited sample sizes in groups studied
- Doses not always directly comparable
- Differences in outcome definitions

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