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Evaluating Predictive Value of Postoperative O_2 Saturation Levels to Rate of Respiratory Safety Events In Oliceridine Trials

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INTRODUCTION

- Postoperative episodes of hypoxemia can be a useful predictor of increased risk of severe respiratory complications that goes largely undetected during routine care.[1]
- Recently, a retrospective observational study reported that early postoperative O_2 desaturation as measured by a nadir oxygen saturation (SpO_2) < 89% or longer duration of O_2 requirement is an independent risk factor of early postoperative respiratory complications and resource utilization.[2]
- Furthermore, documenting SpO_2 < 90% to record ICD-10 code of "acute postprocedural respiratory failure" allows for reimbursement.
- To estimate the impact associated with any postoperative respiratory events following the use of oliceridine in the management of postsurgical acute pain, we propose to include "presence of SpO_2< 90%" as a measure within a health economic model.
- In two randomized, double-blind, placebo- and morphine-controlled phase 3 pivotal studies in patients with moderate to severe acute pain following either orthopedic surgery—bunionectomy, or plastic surgery—abdominoplasty, oliceridine at demand doses of 0.1 mg, 0.35 mg and 0.5 mg provided rapid and effective analgesia compared to placebo.[3,4]
- In these studies, the data collected on respiratory safety events (RSEs) were based on a prespecified definition of RSE [with observations of respiratory rate (RR), SpO_2, somnolence/sedation], as well as verbatim terms coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA), version 19.0.

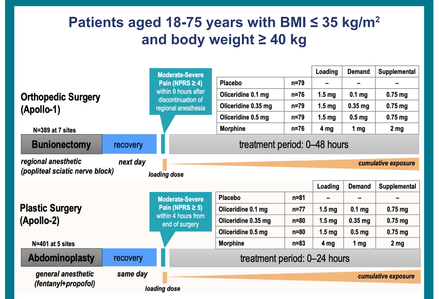
OBJECTIVE

- Here we examined the relationship between RSE and SpO_2< 90% using receiver-operator characteristic (ROC) analysis.

METHODS

- The study designs of the two Phase 3 pivotal trials are shown in **Figure 1**.
- Spontaneously reported adverse events related to RSEs were assessed during the randomized phase and 7-day follow-up period, using the MedDRA version 19.0.

Figure 1: Study Designs of the Phase 3 Pivotal Trials



- In addition, RSE in the protocol was defined as-
  - A clinically relevant worsening of respiratory status.
  - With observations of RR, SpO_2, and somnolence/ sedation (using Moline Roberts Pharmacologic Sedation Scale, MRPSS) performed both at scheduled times and when an RSE was suspected.[3,4]

Analysis

- For this analysis, we evaluated the RSE recorded using the pre-specified definition and examined its relationship with SpO2 using ROC.
- A separate ROC analysis was performed for each of the following variables in order to investigate the predictive strength for detecting an RSE:
  - O2SATRSE (the lowest SpO_2 value recorded prior to the first RSE, or the lowest recorded during the study if there was no RSE);
  - O2AVAL (lowest SpO_2 value recorded during the study);
  - O2SATFL (recorded as 1 if the patient had an SpO_2< 90% anytime during the study, otherwise 0). Since this is a binary variable the ROC analysis was equivalent to utilizing a logistic model;
  - Age, body mass index (BMI) and sex. The baseline age and BMI continuous values were utilized in the ROC analysis. Sex was converted to a numeric binary variable (0=Male and 1=Female) and the ROC analysis was equivalent to utilizing a logistic model.

RESULTS

Patient Demographics

- In both studies, most patients were females, with an average age of 45 years in the orthopedic surgery (bunionectomy) study and 41 years in the plastic surgery (abdominoplasty) study (**Table 1**).
- Nearly 70-75% of patients were Caucasian and the average BMI was 27 kg/m².
- The mean NRS pain intensity score at baseline was 6.7 in the bunionectomy study and 7.3 in the abdominoplasty study.

Table 1: Patient Demographics in the Phase 3 Randomized Controlled Trials

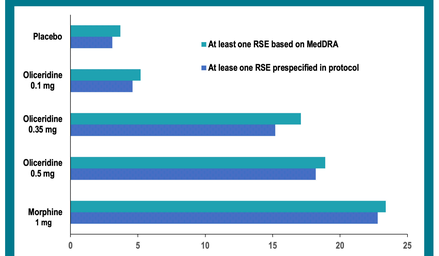
Orthopedic Surgery—Bunionectomy Study					
		Oliceridine demand dose			Morphine
	Placebo N=79	0.1 mg N=76	0.35 mg N=79	0.5 mg N=79	1 mg N=76
Female, n (%)	70 (88.6)	64 (84.2)	65 (82.3)	66 (83.5)	65 (85.5)
Mean (SD) age, years	44.1 (12.6)	47.5 (12.7)	43.6 (13.9)	46.9 (13.8)	43.3 (14.1)
Mean (SD) BMI, kg/m²	26.3 (4.3)	26.4 (4.4)	26.0 (3.8)	27.1 (4.3)	26.5 (4.5)
Race, n (%)					
White	56 (70.9)	47 (61.8)	56 (70.9)	61 (77.2)	50 (65.8)
Black/African American	21 (26.6)	22 (28.9)	17 (21.5)	13 (16.5)	21 (27.6)
Other	2 (2.5)	7 (9.2)	6 (7.6)	5 (6.3)	5 (6.6)
Mean (SD) baseline pain score*	7.0 (1.5)	6.8 (1.8)	6.6 (1.9)	6.5 (1.7)	6.7 (1.6)
Plastic Surgery—Abdominoplasty Study					
		Oliceridine demand dose			Morphine
	Placebo N=81	0.1 mg N=77	0.35 mg N=80	0.5 mg N=80	1 mg N=83
Female, n (%)	81 (100.0)	76 (98.7)	80 (100.0)	80 (100.0)	81 (97.6)
Mean (SD) age, years	42.2 (10.3)	41.8 (10.6)	42.0 (10.0)	40.4 (10.0)	40.4 (10.4)
Mean (SD) BMI, kg/m²	27.0 (3.5)	28.0 (3.4)	27.6 (3.0)	27.0 (3.2)	26.8 (3.3)
Race, n (%)					
White	52 (64.2)	45 (58.4)	55 (68.8)	50 (62.5)	55 (66.3)
Black/African American	27 (33.3)	24 (31.2)	22 (27.5)	28 (35.0)	24 (28.9)
Other	2 (2.5)	8 (10.3)	3 (3.8)	2 (2.5)	4 (4.8)
Mean (SD) baseline pain score*	7.2 (1.4)	7.4 (1.4)	7.4 (1.6)	7.5 (1.6)	7.3 (1.5)

*Patients self rated pain on a numerical rating scale (NRS) from 0 = no pain to 10 = worst pain imaginable

Respiratory Safety Events

- Overall, a lower incidence of RSE was observed with oliceridine (12.8%–13.8%) compared with morphine (22.8%–23.4%).
- The incidence of RSEs using the pre-specified definition matched closely with those reported using MedDRA terms, with discrepancies only in 7 pts (**Figure 2**).

Figure 2: Incidence of Respiratory Safety Events Based on MedDRA Events or as Defined by Measures Prespecified in the Protocol



RSE defined by measures prespecified in the protocol were changes in respiratory rate, oxygen saturation, and sedation measured using the Moline-Roberts Pharmacologic Sedation Scale

- Respiratory Safety events as recorded by the MedDRA events based on standard MedDRA query is shown in **Table 2**.

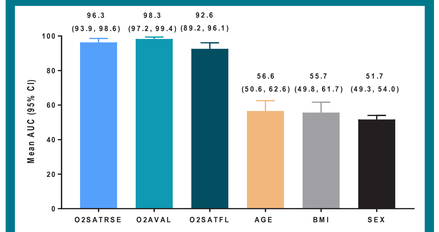
Table 2: Respiratory Safety Events as Recorded by MedDRA Events

Components of RSE n (%)	Placebo	Oliceridine Demand Dose		Morphine	
		0.1 mg	0.35 mg	0.5 mg	1mg
N	162	153	158	159	158
Hypoxia	4 (2.5)	6 (3.9)	20 (12.7)	21 (13.2)	26 (16.5)
O_2 saturation decreased	0	1 (0.7)	4 (2.5)	5 (3.1)	10 (6.3)
Dyspnea	1 (0.6)	1 (0.7)	3 (1.9)	1 (0.6)	1 (0.6)
Bradypnea	0	0	0	2 (1.3)	4 (2.5)
Apnea	1 (0.6)	0	0	0	0
Respiratory Depression/Distress*	0	0	0	3 (1.9)	1 (0.6)

*All patients in the plastic surgery (abdominoplasty trial).
Observations eligible for consideration as respiratory safety events were changes in respiratory rate, oxygen saturation, and sedation measured using the Moline-Roberts Pharmacologic Sedation Scale

- SpO_2 defined in the three ways (**O2SATRSE, O2AVAL, O2SATFL**) was predictive of an RSE, with AUC values ranging from 92.6%–98.3%, the highest value resulting from the O2AVAL definition (**Figure 3**).
- Age, sex and BMI were not predictive of an RSE.

Figure 3: Receiver-operator Characteristic (ROC) Analysis



O2SATRSE	Lowest SpO_2 value recorded prior to the first RSE, or the lowest recorded during the study if there was no RSE
O2AVAL	Lowest SpO_2 value recorded during the study
O2SATFL	Recorded as 1 if the patient had an SpO_2 < 90% anytime during the study, otherwise 0. Since this is a binary variable the ROC analysis was equivalent to utilizing a logistic model
Age, BMI, Sex	The baseline age and BMI continuous values were utilized in the ROC analysis. Sex was converted to a numeric binary variable (0=Male and 1=Female) and the ROC analysis was equivalent to utilizing a logistic model

LIMITATIONS

- The controlled phase 3 oliceridine studies enrolled mostly female patients who were NOT elderly OR obese individuals.
- Thus, the finding of age, sex and BMI not predictive of an RSE cannot be generalized.

CONCLUSION

- Findings from the analysis show a good correlation between SpO2< 90% and spontaneously reported MedDRA RSE as well as the prespecified protocol definition of an RSE.
- Use of SpO_2< 90% appears to be an excellent predictor for modeling the economic outcomes associated with oliceridine and postoperative respiratory complications.

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