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Efficacy and safety of OxyNorm® compared to Morphine sulfate administering through IV continuous infusion in moderate-severe cancer related pain

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1. Introduction

- Morphine has been the treatment of choice for moderate-to-severe cancer pain. However, its use is often hindered by its unpredictable onset of action, inter-individual variability in dose requirements and response[1], and physician concerns about addiction[2].
- Oxycodone, an opioid agonist with affinity for μ and κ receptors[3,4], has been recommended as an alternative to morphine for the treatment of cancer pain[1,5,6].
- Some studies have demonstrated that oxycodone had more rapid analgesic effects[7] and less adverse effects[8] compared with morphine.
- More data is needed to confirm whether oxycodone would present the same efficacy and safety profiles in cancer patients of Asian ethnicity.

Objective:

- To compare the efficacy and safety of oxycodone (Oxynorm®) and morphine administered by intravenous (IV) continuous infusion in Korean patients with cancer pain.

2. Methods

Study Design

- A multi-center, randomized, open-label, active-controlled study conducted at 6 sites in the Republic of Korea from September 2015 to July 2016.
- Patients were randomized to receive either Oxycodone (OxyNorm®) or morphine (BC Morphine Sulfate hydrate injection®)
- The respective analgesics were administered by IV continuous infusion for 5 days. Doses administered were adjusted at the investigator's discretion according to the subject's pain intensity.

Study Assessments

- Average, current, and worst pain intensities for the past 24 hours were evaluated by a 10-point numeric rating scale (0=no pain to 10=worst pain).
- Treatment satisfaction regarding pain was assessed by investigators and patients using a 7-point Global Impression of Change scale (1=Very much improved to 7=Very much worse).

Patients

- **Inclusion criteria:**
  Aged >19 years; diagnosed with cancer; experienced moderate-to-severe pain (NRS≥4) over the past 7 days; hospitalized or scheduled for hospitalization and not planned to be discharged during the study period.
- **Exclusion criteria:**
  Reached the narcotic analgesic dose (oral morphine dose 195 mg/day, oral oxycodone dose 130 mg/day, or patch fentanyl dose 75 μg/hour) for cancer pain prior to screening; medical history of hypersensitivity to oxycodone or morphine or other narcotic analgesics; clinically significant respiratory disorder or severe respiratory dysfunction; on monoamine oxidase inhibitors; moderate-to-severe hepatic impairment i.e. ALT or AST >3.0 upper limit of normal (ULN), total bilirubin >1.5xULN; respiratory depression or hypotension; receiving anticancer therapy; clinically significant cardiovascular or renal dysfunction or pregnancy.

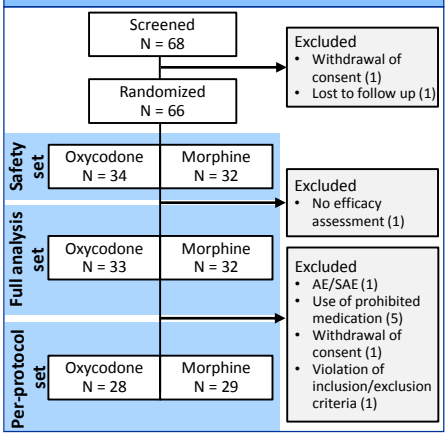
3. Results

Patients

Analysis populations

- Overall, 68 patients were screened **(Figure 1)**
  - Safety set: 66 patients
  - Full analysis set: 65 patients
  - Per-protocol set: 57 patients

Figure 1. Flow of patients through the trial



Patient characteristics (Table 1)

- Average age was 66.6±9.1 years for the oxycodone group and 64.1±13.0 years for the morphine group
- There were no significant differences in age and cancer stage and duration profiles between the groups

Table 1. Patient characteristics (full analysis set)

	Oxycodone (N=33)	Morphine (N=32)
Sex, male, n (%)	21 (63.6)	22 (68.8)
Age, mean±SD, years	66.6 ± 9.1	64.1 ± 13.0
Age distribution, n (%)		
19–39 years	0 (0)	2 (6.3)
40–49 years	1 (3.0)	2 (6.3)
50–59 years	5 (15.2)	6 (18.7)
≥ 60 years	27 (81.8)	22 (68.7)
Weight, mean±SD, kg	58.9 ± 10.1	59.2 ± 12.2
Cancer duration, median (range), months	7.3 (0.1-72.0)	14.5 (0.1-149.0)
Cancer stage, n (%)		
I	0 (0)	0 (0)
II	2 (6.1)	0 (0)
III	4 (12.1)	2 (6.5)
IV	27 (81.8)	29 (93.5)
Unknown	-	1†
Concurrent illnesses, n (%)	28 (84.5)	26 (81.3)
Had chemotherapy 14 days prior to screening till end of study, n (%)	14 (42.4)	18 (56.3)
Had prior medication, n (%)	32 (97.0)	31(96.9)

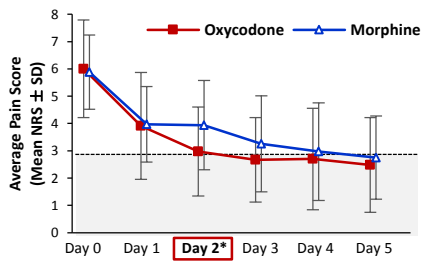
†Morphine group: 1 subject with unknown cancer stage was excluded from percentages calculation.

Efficacy outcomes

Average pain score

- Mean average pain score on Day 2 was significantly lower with oxycodone (3.0±1.6) than with morphine (3.9±1.6; *P*=0.020; **Figure 2**).
- Mean average pain score was ≤3 from Day 2 onwards with oxycodone compared to Day 4 onwards with morphine **(Figure 2)**
- By day 5, both groups achieved >50% reduction in mean average pain score (oxycodone vs morphine: -56.7% vs -52.9%; *P*=0.553)
- Changes in average pain score from baseline to Day 5 were not significantly different between the groups
  - Full analysis set: -3.52 vs -3.13, *P*=0.562
  - Per-protocol set: -3.29 vs -3.17, *P*=0.961

Figure 2. Average pain scores (full analysis set)

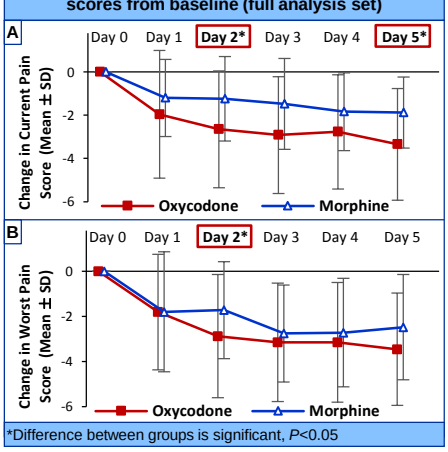


*Difference between groups is significant, *P*<0.05

Current and worst pain score

- Mean reduction in current pain score was significantly larger with oxycodone than with morphine on Day 2 and Day 5 **(Figure 3A)**
- Mean reduction in worst pain score was significantly larger with oxycodone than with morphine on Day 2 **(Figure 3B)**

Figure 3. Change in (A) current and (B) worst pain scores from baseline (full analysis set)



*Difference between groups is significant, *P*<0.05

Treatment satisfaction

- By Day 3, most patients (95.3%) and investigators (96.9%) reported some improvement in pain relief regardless of the pain medication
- There were no differences in treatment satisfaction scores reported by patients and investigators for both oxycodone and morphine

Treatment dose

- Mean cumulative doses of oxycodone and morphine at the end of the study (Day 5) were 226.8±110.4 mg and 226.6±135.1 mg (*P*=0.996) respectively.
- There were no differences in the cumulative doses given to each group on a daily basis during the study period

Safety outcomes

Adverse events

- There were no significant differences between the groups with respect to the incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, and unexpected drug reactions **(Table 2)**
- The most commonly reported adverse event in both groups was gastrointestinal disorders, mostly due to constipation (oxycodone, 13/34; morphine, 6/32) and nausea (oxycodone,10/34; morphine, 8/32)
- Significantly more unexpected adverse events were reported with morphine than with oxycodone (*P*=0.049; **Table 2**)

Table 2. Incidence of adverse events (safety set)

	Oxycodone (N=34)	Morphine (N=32)	*P*
AEs	29(85.3)	26(81.3)	0.66
Unexpected AEs	9(26.5)	16(50.0)	**0.049**
Blood & lymphatic system disorders	3(8.8)	1(3.1)	
Gastrointestinal disorders	2(5.9)	5(15.6)	
Metabolism & nutrition disorders	2(5.9)	2(6.3)	
Injury, poisoning & procedural complications	2(5.9)	0	
Respiratory, thoracic & mediastinal disorders	1(2.9)	4(12.5)	
Infections/infestations	1(2.9)	2(6.3)	
Investigations	1(2.9)	1(3.1)	
General disorders & administration site	0	5(15.6)	
Renal & urinary disorders	0	3(9.4)	
Other disorders	0	2(6.3)	
Dropouts*	2(5.9)	0(0.0)	0.493†
Serious AEs	3(8.8)	2(6.3)	>0.999†
ADRs	14(41.2)	11(34.4)	0.569
Serious ADRs	0(0.0)	0(0.0)	-
Unexpected ADRs	0(0.0)	1(3.1)	0.485†

Data presented as n (%). *Dropouts caused by AEs are subjects whose reason for dropout was 'difficult to perform the study due to AE or serious AE'; †Exact test. AE, adverse event, ADR, adverse drug reaction.

4. Conclusions

- IV oxycodone showed similar analgesic efficacy and safety profile as IV morphine in Korean patients with moderate-to-severe cancer pain
- Oxycodone was found to be faster acting and can be a good alternative to morphine for the treatment of moderate-to-severe cancer pain

Acknowledgments

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5. References

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