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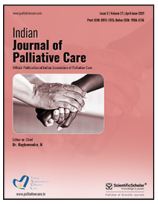
Indian Journal of Palliative Care



*Short Report*

# Effectiveness of Morphine in Managing Refractory Dyspnoea in Patients with Coronavirus Disease (COVID-19)

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## ABSTRACT

Opiates are generally used to relieve dyspnoea in advanced diseases such as cancer and lung diseases. However, little is known regarding the safety and efficacy of morphine for refractory dyspnoea in coronavirus disease 2019 (COVID-19) patients. We retrospectively reviewed records of 18 COVID-19-positive patients who were administered morphine for refractory dyspnoea during hospitalisation between May 2021 and June 2021. Details of morphine usage, vital signs, an 11-point dyspnoea numeric rating scale (DNRS) and adverse events at baseline, 24 h and 72 h after the start of treatment were abstracted from records. The final clinical outcome in terms of death or discharge was noted. All patients had severe refractory dyspnoea (DNRS score ≥7) at the time of administration of morphine and had not been relieved from standard care for the past 3 days. In the results, the mean (standard deviation [SD]) age was 47.1 (12) years, male was 13 (72.20%) patients and modified Medical Research Council Grade 4 was present in all 18 patients. The mean (SD) 1st day dose of morphine was 7.03 (1.53) mg and the mean (SD) duration of morphine use was 5.22 (3.00) days. Significant decreases in DNRS, respiratory rate and oxygen saturation were observed 24 h and 72 h after the start of morphine administration. Meanwhile, blood pressure and heart rate were not significantly altered after treatment. The finding of this single-centre retrospective study indicates that morphine may be considered for use in the management of refractory dyspnoea among COVID-19 patients.

**Keywords:** Morphine, Breathlessness, Dyspnoea, Coronavirus disease 2019

## INTRODUCTION

Difficulty in breathing or dyspnoea is a subjective experience in which the patient has air hunger, increased breathing effort, tightness of chest, rapid breathing and suffocation feeling. Dyspnoea is a multidimensional symptom, consisting of multiple factors such as physiological, psychological and environmental.[1,2] The severity of breathlessness cannot be determined from physical examination or laboratory findings. It can occur in the absence of physical signs such as rapid, deep or laboured breathing or absence of any abnormal findings on blood gas examination or chest x-rays.[3] One of the common symptoms of coronavirus disease 2019 (COVID-19) is dyspnoea. Mild dyspnoea is common but there is a concern when there is worsening dyspnoea, dyspnoea at rest and increased severe chest discomfort/tightness.[4,5] The timeline of dyspnoea is important, as acute respiratory distress syndrome (ARDS) manifests soon after the onset of dyspnoea. A study demonstrates that after the onset of dyspnoea, ARDS develops after a median of 2.5 days.[6] Opiates are generally used to reduce the perception of breathlessness in advanced diseases such as cancer and lung diseases, including chronic obstructive lung disease.[7] In COVID-19 patients, standard therapy that usually includes oxygen, steroids, bronchodilators, anticoagulants and adjuvant treatment (other than opioid therapy) may sometimes be unable to control dyspnoea.[8] In these patients, morphine can be given in addition to standard treatment to relieve respiratory symptoms. In this retrospective study, data were collected for 18 patients in whom morphine in addition to standard treatment was given to relieve dyspnoea.

## METHODS

### Study design and population

This was a single-centre retrospective study conducted in the National Cancer Institute (All India Institute

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**Received:** 10 May 2021 **Accepted:** 16 July 2022 **EPub Ahead of Print:** 25 August 2022 **Published:** 23 November 2022 **DOI:** 10.25259/IJPC_112_2022

of Medical Sciences, New Delhi), which is an apex care institute in India. This study was approved by the Institutional Ethics Committee of the institution. In a total of 25 COVID-19 patients who received morphine for the management of refractory dyspnoea in the intensive care unit (ICU) of our institution, clinical records with study variables of interest were available for 18 patients and were included for analysis. The decision to administer morphine to COVID-19 patients with intractable severe dyspnoea that was refractory to standard care approaches was made by the multidisciplinary team of senior physicians and attending doctors. The dose and duration of morphine therapy were determined on a case-by-case basis considering the age and symptom severity of the patients. All patients had severe refractory dyspnoea with respiratory rate >24 breaths/min and oxygen saturation <94% not relieved from standard care from the past 3 days.

### Measurements

Dyspnoea, measured on a dyspnoea numeric rating scale (DNRS), is recorded in the medical charts as per institutional ICU protocol.[9] It is a 0–10-point scale where 0 represents 'Not breathless at all' and 10 represents 'Breathlessness as bad as you can imagine'. DNRS scores at baseline, 24 h and 72 h from the morphine administration were obtained from the medical charts. Detailed data on morphine usage including the administration route, dose and duration were also noted. Temporal changes in vital signs including respiratory rate, oxygen saturation, blood pressure and heart rate were calculated with baseline value as a reference. The presence of respiratory depression defined as a respiratory rate of <10 breaths/min. Symptom scale data before starting treatment and about 24 and 72 h after starting morphine were also obtained.

Adverse events due to morphine usage, including nausea, vomiting, constipation, respiratory depression and delirium, at baseline and within 24 and 72 h after starting morphine, were captured along with the reason for discontinuation if morphine was discontinued. We noted total morphine consumption per day for 3 consecutive days. Patient outcomes in terms of progression to mechanical ventilation and discharge or death were captured. Laboratory parameters at the time of morphine administration and within 24 and 72 h after starting morphine were obtained. Severe liver dysfunction was defined as newly developed liver enzyme elevation (total bilirubin >3 upper limits of normal, aspartate aminotransferase or alanine aminotransferase >5 upper limits of normal) and severe kidney injury was defined as an increase of serum creatinine more than 3 times of baseline level.

### Statistical analysis

Continuous measures were described using means and their standard deviation (SD) and categorical measures by proportions. Mean differences in the DNRS, respiratory rate, oxygen saturation and vitals at 24 h and 72 h intervals from the baseline values were calculated. One sample *t*-test or Wilcoxon sign-rank test was used to examine if the mean of these measures at 24 and 72 h varied significantly from that of the baseline measure.

## RESULTS

During the study period, a total of 18 COVID-19 patients were administered morphine for refractory dyspnoea in addition to standard care. Demographic and clinical characteristics of patients are presented in Table 1. The mean (SD) age was 47.1 (12) years and 13 patients were male (72.20%). All patients had a modified Medical Research Council grade of 4.[10] No patient was on any inotropes or vasopressors. No patients with liver and renal dysfunction were given morphine for dyspnoea. The average hospitalisation period of the study cohort was 17.39 (11.87) days with a mean of morphine use was 5.22 (3.00) days.

The average dose of morphine used on day 1, 2 and 3 is 7.02 (1.52), 5.91 (2.92) and 5.91 (3.25) mg, respectively. Means of DNRS, respiratory rate, $SpO_2$ and vital parameters at intervals after treatment and their difference from baseline at these intervals are shown in Table 2. Significant decreases in DNRS, respiratory rate and oxygen saturation

**Table 1:** Sample characteristics.

| Variable | Sample distribution (*n*=18) |
|---|---|
| Age (Mean [SD]) | 47.1 (12) |
| Sex (*n* [col %]) | |
| Female | 5 (27.8) |
| Male | 13 (72.2) |
| Oxygen support | |
| HFNC | 11 (61.1) |
| NRBM | 7 (38.9) |
| Baseline clinical parameters (Mean [SD]) | |
| Heart rate | 81.8 (5.7) |
| Systolic BP | 130.9 (12.9) |
| Diastolic BP | 77.1 (4.8) |
| Respiratory rate | 28.4 (1.6) |
| % $SpO_2$ | 91.7 (1.3) |
| NRS (Median [IQR]) | 7 (7-8) |
| Baseline laboratory parameter (Mean [SD]) | |
| Haemoglobin | 11.6 (1.6) |
| Platelet count | 158,529.4 (52,590.5) |
| Creatinine | 0.8 (0.2) |
| Urea | 40.3 (12.7) |
| Baseline inflammatory markers (Median [IQR]) | |
| Total leucocyte count | 11,700 (11,300–12,300) |
| D-Dimer | 677 (545–997) |
| IL-6 | 23 (12–33) |
| CRP | 6 (3–11) |

CRP: C-reactive protein, IL: Interleukin, BP: Blood pressure

**Table 2:** Mean difference in parameters from baseline at 24 h and 72 h.

| Parameter | 24 h | Mean difference (95% CI) | *P*-value | 72 h | Mean difference (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| NRS | 4.00 (1.78) | −3.39 (−4.26–−2.52) | <0.001* | 2.67 (0.49) | −4.67 (−5.07–−4.27)) | 0.001* |
| Respiratory rate | 24.06 (3.02) | −4.33 (−5.95–−2.75) | 0.001* | 23.39 (3.33) | −5.00 (−6.65–−3.35) | <0.001* |
| SpO2 | 93.00 (1.85) | 1.28 (0.58–1.97) | 0.004* | 93.67 (1.88) | 1.94 (1.11–2.77) | 0.001* |
| HR | 80.21 (5.82) | −1.61 (−3.40–0.18) | 0.088* | 81.2 (7.03) | −0.56 (−2.99–1.88) | 0.498* |
| Systolic BP | 128.61 (13.16) | −2.33 (−5.14–0.47) | 0.097 | 128.67 (12.56) | −2.28 (−5.01–0.46) | 0.097 |
| Diastolic BP | 75.67 (4.80) | −1.44 (−2.97–0.08) | 0.062 | 76.17 (5.34) | −0.94 (−2.11–0.22) | 0.105 |

Mean difference is from baseline value. *Wilcoxon sign-rank *P*-values

were observed 24 h and 72 h after the start of morphine administration. Other vital signs including blood pressure and heart rate were not significantly altered 24 and 72 h after starting morphine. No severe liver dysfunction and kidney injury related to morphine occurred within 72 h after morphine therapy.

Of the 18 patients in our study sample, morphine was discontinued in 3 (16.67%) patients before 72 h. The reasons for discontinuation were as follows: Intractable vomiting in two and clinical deterioration in one patient. Among 18 patients, 1 (5.55%) died during hospitalisation on the 25$^{th}$ day of hospital admission. Seventeen patients (94.44%) got discharged from the hospital (two patients out of 17 were sent to the pulmonary medicine ward for pulmonary rehabilitation and subsequently discharged from there). Two patients reported constipation that was medically managed by laxatives.

## DISCUSSION

Morphine could have a beneficial effect by mitigating the cytokine storm in the early stages of severe COVID-19. In contrast, it could be potentially harmful in the late stages of severe COVID-19, especially in the presence of septic shock.[11] In this retrospective study, morphine was given for refractory dyspnoea. Initially, morphine was administered as a low dose and titrated as per patient response. Dyspnoea significantly decreased 24 h after starting morphine therapy. Some patients discontinued morphine and have few non-serious adverse events.

Morphine has been studied as an effective modality for cancer dyspnoea and chronic obstructive pulmonary disease.[7,12,13] The perception of breathlessness decreased at a lower dose of morphine than those required to alleviate pain. In our study, we also used a very low dose of morphine to alleviate the perception of breathlessness. There is limited literature about morphine administration for refractory dyspnoea in COVID-19. Ours is a retrospective study, so optimal dose and timing of morphine administration cannot be commented on and these should be further investigated in a future study.

The effects of opioids for dyspnoea are assumed to be multifactorial, including decreasing respiratory drive, altering central perception and alleviating anxiety.[14] Opioid therapy may offer hope in refractory dyspnoea in COVID-19 patients as well. However, trials of the use of opioids for the relief of dyspnoea in COVID-19 have been sparse. The previous studies suggested that opioids were not associated with reduced survival in terminally ill cancer patients. Our study in COVID-19 patients also revealed that an opioid did not significantly affect vital signs including blood pressure, heart rate and oxygen saturation at least within 72 h, suggesting the short-term safety of morphine administration.

### Study limitations

This study had several limitations. First, this was a single-centre retrospective study with relatively small sample size. The frequency of symptom evaluation, data entry and titration of morphine highly varied because of the high patient load during the second wave of COVID-19 in India. We judged the adverse events retrospectively based on the description in the medical records.

## CONCLUSION

This single-centre retrospective study suggested that low-dose morphine may be given for the treatment of refractory dyspnoea in COVID-19 patients.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Sirohiya P, Pandey K, Sagiraju HK, Bhatnagar S. Effectiveness of morphine in managing refractory dyspnoea in patients with Coronavirus disease (COVID-19). Indian J Palliat Care 2022;28:443-6.