THE ROLE OF OPIOID IN RELIEVING BREATHLESSNESS IN ADVANCED DISEASE

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ABSTRACT

Introduction: *More than half of patients with advanced disease have difficulty breathing, and this chronic breathlessness can be highly debilitating and challenging to manage. Opioids are the pharmacological drug that usually used for the palliation treatment of breathlessness, although their mechanism of action is still not completely known.*

Methods: *We searched for literatures from several databases, which were: Pubmed, Cochrane Review, and Scopus with keywords: (opioid OR morphin) AND (breathlessness OR dyspnea) AND (advanced disease). The search was conducted on September, 27st 2018. The inclusion criteria were: human study, publication within the last 5 years, English language, randomized controlled trial, meta-analysis, and systematic review. The recruited literatures were appraised using clinical epidemiology and evidence based medicine (CEEBM) worksheet.*

Results: *Literature searching from three previously stated databases revealed only one article which were found to fulfill the inclusion criteria. From the review, for the primary outcome of breathlessness, the mean post-treatment dyspnoea score was 0,28 points better in the opioids group. The mean change from baseline dyspnoea score was 0,09 points better in the opioids group, but both of them have low quality evidence.*

Conclusion: *There is some low quality evidence that shows benefit for the use of oral or parenteral opioids to reliev breathlessness in advanced disease, although the number of included participants was small. In the sub group analysis, there is a strong treatment effect for morphine to relieve breathlessness. We found no evidence to support the use of nebulised opioids. Further research with larger numbers of participants, using standardised protocols and with quality of life measures included, is needed.*

Keywords: *advanced disease, breathlessness, opioid*

ABSTRAK

Pendahuluan: Lebih dari setengah pasien dengan penyakit lanjut memiliki kesulitan dalam bernapas. Hal ini sangat mengganggu dan menjadi tantangan untuk ditangani. Opioid merupakan obat yang biasanya digunakan pada penatalaksanaan sesak yang paliatif.

Metode: Kami mencari literatur dari beberapa *database* seperti Pubmed, Cochrane Review, and Scopu sdengan kata kunci *(opioid OR morphin) AND (breathlessness OR dyspnea) AND (advanced disease)*. Pencarian dilakukan pada 27 September 2018. Kriteria inklusi adalah studi pada manusia, publikasi dalam 5 tahun terakhir, bahasa Inggris, *randomized controlled trial*, metaanalisis, atau telaah sistematik. Literatur akan dinilai dengan *clinical epidemiology and evidence based medicine (CEEBM) worksheet.*

Hasil: Terdapat satu artikel yang memenuhi kriteria. Hasil telaah menunjukkan bahwa rerata skor dispnea post terapi 0,28 lebih baik pada grup dengan pemberian opioid. Perubahan

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rerata skor dispnea dari *baseline* 0,09 lebih baik pada grup opioid. Namun kedua hasil tersebut memili kualitas bukti yang rendah.

Kesimpulan: Terdapat beberapa bukti dengan kualitas yang rendah yang menunjukkan keuntungan pemberian opioid oral atau parenteral untuk mengurangi sesak pada penyakit lanjut. Pada analisis subgrup, terdapat efek terapi yang kuat pada morfin untuk mengurangi sesak. Kami tidak menemukan bukti yang mendukung pemakaian nebulisasi opioid. Penelitian lebih lanjut dibutuhkan dengan jumlah sampel yang lebih banyak dan penggunaan protokol yang terstandarisasi.

Kata kunci: *advanced disease*, sesak, opioid

BACKGROUND

More than half of patients with advanced disease have difficulty breathing, and this chronic breathlessness can be highly debilitating and challenging to manage.[1] Breathlessness is prevalent in 50% to 60% of patients with advanced disease generally and in up to 74% of patients with lung cancer or metastatic cancer in the lung.[1] Prevalence increases during the last 6 weeks of life and can cause significant psychological and emotional distress.[1] Chronic refractory breathlessness can lead to overwhelming feelings of helplessness, anxiety, and depression.[2] Qualitative data have shown that the symptom can be described along three dimensions: air hunger, the need to breathe while being unable to increase ventilation, effort of breathing or physical tiredness associated with breathing, chest tightness or the feeling of constriction and inability to breathe in and out.[2]

Since breathlessness is completely subjective in perception, the most valid assessment instrument is the patient-reported outcome addressing the multidimensional and multifactorial nature of the symptom.[2] If this is impossible due to impaired communicative capability of the patient, relative or caregiver, reported breathlessness may be helpful.[2] The differentiation between continuous, episodic, breakthrough or crisis breathlessness, as well as the evaluation of onset, exacerbating and relieving factors is important in order to adjust the therapy appropriately, taking into consideration disease-modifying, causative and symptomatic treatment options.[3] Breathlessness often leads to severe anxiety but severe anxiety can cause breathlessness as well.[3] Therefore, the psychosocial dimension and environmental conditions should not be omitted and very often play a major role in the clinical condition.[3]

Opioids are the pharmacological drug that usually used for the palliation treatment of breathlessness.[4] They can be used in opioid-naive as well as in opioid-tolerant patients without causing relevant breath depression or impaired oxygenation or increase in CO2 concentration.[4] Nevertheless, patients receiving opioids for breathlessness experience the well-known opioid-related unwanted side effects, e.g. initial nausea and persistent constipation.[4] Exogenous and endogenous opioids specifically bind to the μ receptors to reduce transmission of pain signals. Opioids also depress respiratory drive by directly blunting the responsiveness of the brainstem centres, which are affected by hypoxia and hypercapnia.[4] Decreased respiratory output results in a decrease in corollary discharge from the brainstem to perceptual areas in the cerebral cortex and thus reduced the sensation of breathlessness.[4] Corollary discharge describes the hypothesis that a sensory 'copy' of the motor output is sent from the motor cortex to the sensory cortex and imparts a conscious awareness of respiratory effort.[4] Opioids may also cause blunting of perceptual sensitivity to sensations of breathlessness.[5] Neuroimaging studies demonstrate that opioid receptor agonists can modulate the central processing of breathlessness similar to that of pain relief.[5] Administration of opioids stimulate activity in the anterior cingulate cortex, thalamus, frontal cortex, and brainstem, the same areas which are activated when breathlessness occurs.[5] Peripheral opioid receptors are located in bronchioles and alveolar walls of the respiratory tract.[5] Opioid administration may modulate breathlessness by binding to these opioid receptors. It is theorised that opioid administration could modulate breathlessness by binding to these peripheral opioid receptors.[5]

Beside its benefit, opioid has side effects that must be considered including drowsiness, euphoria, confusion, peripheral vasodilation, constipation, nausea and vomiting.

Subcutaneously and intravenously applied opioids are effective, with the intravenous form having the most rapid onset.[4] There is no evidence for the efficacy of nebulised or inhaled opioids.[6] Some guidelines recommend opioids as the first-line pharmacological treatment for breathlessness.[6] A Cochrane review published in 2001 concluded that there was some evidence to support the use of oral and parenteral opioids to palliate breathlessness, but the number of participants studied was small and they recommended that larger trials were needed using standard protocols and incorporating quality of life measures. This evidence based case report was written to prove that opioids has efficacy and safety to relieving breathlessness in patient with advanced disease.

CASE ILLUSTRATION

A 53 years old male came to the emergency department of Cipto Mangunkusumo National Hospital (RSCM) with a chief complaint of breathlessness that gradually increased since 1 week before hospital admission. He also complained bleeding of scapulae tumor that was diagnosed with angiosarcoma, 1 year ago from the biopsy. He had fever sometimes, productive cough, decreased appetite, and unmeasured weight loss. He has been treated in RSUD Serang for 2 weeks before admitted to RSCM, where he was given packed red cells because of her low hemoglobin. In RSUD Serang, she also had tumor bleeding and difficulty to move his left arm because of the tumor mass. Because the breathlessness did not relieve, she was referred to RSCM with a working diagnosis of angiosarcoma with suspected lung metastasis. The patient was then admitted to the 5th floor of Building A RSCM. There was no previous history of diabetes mellitus, hypertension, cardiac disease, renal disease, liver disease, or allergy. There was no family history of similar disease with the patient, malignancy, or other chronic diseases. Patient was a husband with three children, never smoked, and no exposure to alcohol, traditional medicine, or herbal medications.

On physical examination, the patient appeared moderately ill, fully alert and compos mentis with GCS 15, the hemodynamic was still stable with blood pressure 130/80 mmHg, heart rate 95 times/minute, temperature 36,8°C, respiratory rate 28 times/minute, and peripheral oxygen saturation 98% with 3 lpm nasal cannula. The abnormalities found on physical exam were anemic conjunctivae, poor oral hygiene, bilateral chest rales, epigastric abdominal pain, and there was a tumor mass in the left scapulae that was easy to bleed.

The laboratory examination results showed Hb 11,2, Ht 33,2%, leucocytes 15.800, and thrombocytes 137.000, with neutrophilia. The hemostasis parameters were under the upper limit value (PT/INR 1,07 times from control, APTT 1,1 times from control, and D-dimer 5,2). The biopsy of the tumor mass showed an angiosarcoma. Chest x-ray showed bilateral pulmonary infiltrates and coined lesion in the apex.

Patient was consultated to palliative team and was treated with intravenous morphin 5 mg/24 hours to relieve the breathlessness. Patient was also gave broad spectrum antibiotics, and a few of symptomatic medicines. After 10 days of care, the symptom of breathlessness in the patient was better, and patient finally went out for homecare program. Encouraged by the question, we started to search for evidence regarding the role of opioids in relieving breathlessness in advanced diseases.

Clinical Question

In advanced diseases, Are opioids effective in relieving breathlessness?

P : advanced diseases
I : Opioids
C : placebo or other drugs
O : relieving breathlessness

METHODS

Search Strategy

We searched for literatures from several databases, which were: Pubmed, Cochrane Review, and Scopus with keywords: (opioid OR morphin) AND (breathlessness OR dyspnea) AND (advanced disease). The search was conducted on September, 27st 2018. The inclusion criteria were: human study, publication within the last 5 years, English language, randomized controlled trial, meta-analysis, and systematic review.

Critical Appraisal

Critical appraisal was done by using Clinical Epidemiology and Evidence Based Medicine (CEEBM) worksheet for appropriate study design found from the literature search, which were meta-analysis/systematic review studies. There was no recent randomized clinical trial about our topic in the last five years, and therefore we only used studies with meta-analysis/systematic review designs. Every study was assessed by its validity, importance, applicability, and level of evidence.

RESULTS

Literature searching from three previously stated databases revealed only one article which were found to fulfill the inclusion criteria. Two studies were excluded because of different study purposes, two studies were also excluded due to different comparison of intervention, two studies had no full text available, and two studies were excluded because they were not systematic review nor meta-analysis design (table 1 and figure 1).

Table 1. Literature search strategy used for several databases.

Database	Keywords	Results	Articles
Pubmed	(opioid OR morphin) AND (breathlessness OR dyspnea) AND (advanced disease)	92	1
Cochrane Review	(opioid OR morphin) AND (breathlessness OR dsypnea) AND (advanced disease)	2	1
Scopus	(opioid OR morphin) AND (breathlessness OR dyspnea) AND (advanced disease)	0	0

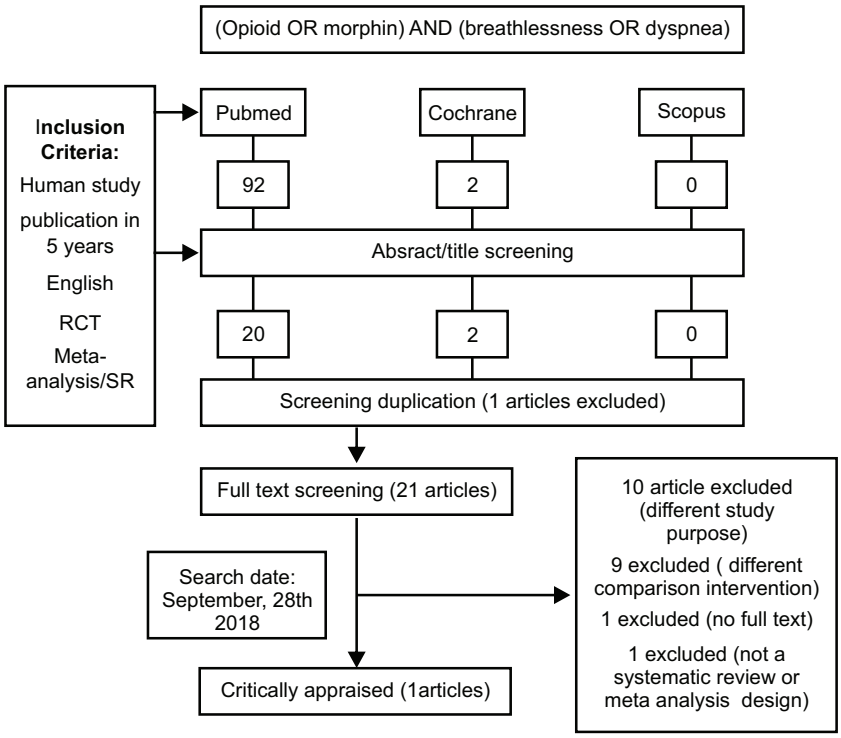

Figure 1. Search Strategy Flowchart

Table 2. Critical appraisal results of the included studies using CEEBM worksheet for systematic review/meta-analysis studies

No	Authors	Validity				Importance	Applicability				Level of Evidence
		Systematic review from randomized trials	All relevant	Assessment of validity trial	Consistency	Standardised Mean Differences	Different from our patient	Benefit for every patient	Clear value and preferences	Benerfit more than risk	
1	Barnes H, et al (2008)	(+)	(+)	(+)	(+)	*	(+)	(+)	(+)	(+)	Low

* For the primary outcome of breathlessness, the mean post-treatment dyspnoea score was 0,28 points better in the opioid group compared to the placebo group.
* For the primary outcome of breathlessness, the mean change from baseline was 0,09 points better in the opioid group compare to the placebo group.

Table 3. Summary of the included studies

No.	Author	Study design	Subject numbers	Inclusion criteria	Exclusion criteria	Study results	
1	Barnes H, et al	Systematic review and meta-analysis	18 studies (266 patients)	Randomized studies with parallel control group, which recruited adult with refractory breathlessness in advanced disease that receiving Opioids (intervention) or placebo (control), and assessed breathlessness as the primary outcome.	Pediatric population, quasi-randomized trials, observational studies, other interventions, review/ editorial/case reports.	The meta-analysis demonstrates a small treatment effect for breathlessness (change from baseline, seven studies, 107 participants; SMD –0,09, 95% (CI) ⁻0,36 to 0,19; P=0.54, post-treatment score, 11 studies, 159 participants, SMD ⁻0,28,95% CI –0.50 to ⁻0.05; P = 0.02)	Risk of bias was variable in the included studies, The strength of the evidence available is limited by the small sample size of the studies, and by the variability of outcome measures utilised, which limits meta-analysis. Quality and applicability of evidence is also limited in that studies measured the response to intervention shortly after administration.

DISCUSSION

This systematic review demonstrates low quality evidence for a small clinically significant effect for oral and parenteral opioids compared to placebo in the relief of breathlessness. The strength of the evidence available is limited by the small sample size of the studies, which involved six to 63 participants with a mean of 19 participants per study, and by the variability of outcome measures utilised, which limits meta-analysis.[6] Quality and applicability of evidence is also limited in that studies measured the response to intervention shortly after administration, in a crossover study design, often conducted on two consecutive days with the intervention on one day and control the next.[6] Few studies involved multiple doses or titration according to the participants individual response. This may introduce a unit-of-analysis error, the confidence intervals (CIs) may be too wide, and the data may be under weighted, thus disguising clinically important heterogeneity. The data was analysed using a fixed-effect model due to concerns regarding small-study bias, and this may underestimate clinically important differences.

There is insufficient evidence at this level to suggest that nebulised opioids are more effective than placebo in relieving breathlessness. This may be explained by the difference in pharmacodynamics of opioids. Not all opioids can be administered via inhaled or intranasal modes. In order to be absorbed by the intranasal or intraoral mucosa, opioids need to be lipophilic. The lack of evidence for nebulised studies may be influenced by the lack of consistency between studies, as nebuliser devices between different studies were not randomised, and particle size and distance from device to mouth varied. Therefore the total amount of opioid reaching the lungs may have varied. The conclusions we can draw from this review are limited to the dosages used in the included studies. The included studies used a wide range of doses, thus an enhanced effect may be seen with higher doses.

However, the risk of adverse events, including constipation, may also increase.[6] The studies on breathlessness used a variety of different outcome measures, including the Borg and visual analogue scale (VAS).[6] The point at which studies measured the data also varied, and may or may not have included an exercise test. The studies reported data variably as either a change from baseline or post-treatment change. This variability in data reporting causes difficulty in interpretation, therefore it is recommended that future studies standardize outcome measures. Not all studies reported adverse outcomes. The most common symptom was drowsiness, followed by nausea and vomiting, and constipation. Adverse effects caused some participants to withdraw from the trial. These trials used high doses of morphine at 20 mg oral morphine daily or more.[6] Further research is required to determine if the same improvement of breathlessness can be achieved at lower doses with a reduction in adverse events. Very few studies included data on quality of life. This is an important omission as the participants in these studies were all symptomatic, thus quality of life data are particularly relevant.

From the subgroup analysis we concluded that there was a strong treatment effect for morphine to relieve breathlessness and there were no effect for hydromorphone, oxycodone and fentanyl, if were compared with the placebo to reliev the breathlessness. There were insufficient data to suggest opioids would be more beneficial in any specific condition such us COPD and advanced cancer. There was no significant difference overall for heart failure. This review also examined the use of opioids compared to other interventions. This review included one study, Navigante 2010, which found that opioids were inferior when compared to intravenous midazolam for the relief of breathlessness.[6]

This systematic review only included randomised controlled trials (RCTs), however 17 out of 26 studies had an unclear risk of bias overall, mostly due to inadequate reporting of randomisation and allocation sequence.[6] This review included double blind RCTs, however two studies were only single blinded.[6] There was significant heterogeneity between studies for the main outcome of breathlessness (I^2 statistic =74%, P = 0.0009), which may be explained by the small sample size and inconsistency with outcome measures.[6] Therefore, these results

should be interpreted with caution. There was a risk of imprecise results due to the low numbers of included participants. For these reasons the quality of the evidence was low for breathlessness posttreatment score, and very low for breathlessness change from baseline. Further research using larger studies for longer duration, with consistent outcome measures, and adequate randomisation and blinding, is likely to have an important impact on our confidence in the estimate of effect and likely to change the estimate. Publication bias is possible, whereby a failure to identify unpublished negative trials could have lead to an overestimation of the effect of opioids for breathlessness.[6] This may introduce a unitof-analysis error, the CIs may be too wide, and the data may be under-weighted, thus disguising clinically important heterogenity.[6]

CONCLUSION

There is low quality evidence showing benefit for the use of oral or parenteral opioids for the relief of breathlessness in some adults with advanced disease and terminal illness. The morphin has better effect to relieve breathlessness than other opioids. Based on this evidence, it is possible that opioids lead to short-term increase in exercise capacity. It is difficult to draw firm conclusions about the clinical significance of the pooled estimate of treatment effect in this meta-analysis as we used standardised mean difference (SMD) values to combine studies due to the lack of standardized outcome measures but the magnitude of the treatment effect appears small. There is no evidence to support the use of nebulised opioids for the treatment of breathlessness.

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