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Extended-release morphine for chronic breathlessness in pulmonary arterial hypertension – a randomised, double-blind, placebo-controlled, crossover study

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Abstract

Context: Pulmonary arterial hypertension (PAH) affects people of all ages and is associated with poor prognosis. Chronic breathlessness affects almost all people with PAH.

Objectives: This randomised, placebo-controlled, double-blind, cross-over study aimed to evaluate the effects of regular, low-dose, extended-release (ER) morphine for PAH-associated chronic breathlessness.

Methods: Participants with PAH-associated chronic breathlessness were randomised to i) seven days ER morphine 20mg, ii) seven-day washout and iii) seven days of identically-looking placebo, or vice-versa. Primary endpoints were breathlessness "right now" - morning and evening - measured with a visual analogue scale. Secondary endpoints included additional breathlessness measures, quality of life, function, harms and blinded treatment preference (ACTRN12609000209291).

Results: Within a period of 7 years, 50 patients were assessed in detail and 23 (46%) were randomised (despite broad eligibility criteria). Four participants withdrew while taking morphine. Nineteen participants completed the study. Breathlessness "right now" was higher on morphine compared with placebo both for morning [mean (M) ± standard deviation (SD) 31.7 ± 25 mm vs. 26.9 ± 22 mm; effect size (80% CI) = -0.22 (-0.6 to 0.2)] and evening [(M±SD 33.5 ± 28 mm vs. 25.6 ± 21 mm; effect size (80% CI) = -0.33 (-0.8 to 0.1)]. All secondary measures of breathlessness were higher with morphine as were nausea and constipation.

Conclusions: This study does not support a phase III study of ER morphine for people with PAH-associated chronic breathlessness. Recruitment was challenging, the direction of effect in every measure of breathlessness favoured placebo and morphine generated more harms.

Key words: Chronic breathlessness, pulmonary arterial hypertension, morphine, randomised controlled trial, effectiveness study

Running title: Extended-release morphine for breathlessness in PAH

Introduction

Pulmonary arterial hypertension (PAH) is a “chronic disorder of the pulmonary vasculature” [1] characterised by increased pressure in the pulmonary artery (≥ 25 mmHg at rest) [2]. According to the World Health Organization (WHO) classification, PAH corresponds to the first diagnostic group of pulmonary hypertension which includes idiopathic PAH; heritable PAH; and PAH secondary to drugs/toxins and systemic conditions [1]. Although rare, PAH can affect adults of all ages [3] and has a poor prognosis with a 5-year survival rate of 57% after diagnosis [4].

Breathlessness affects approximately 98% of people with PAH and it is both the earliest and the most prevalent symptom [5]. For many patients with advanced disease, PAH-specific treatments fail to provide adequate symptom relief and breathlessness becomes chronic [6]. Chronic breathlessness is highly distressing [7] and demands a specific clinical approach that treats the symptom at the same time as underlying aetiologies.

Regular, low-dose oral, extended-release (ER) morphine may relieve chronic breathlessness in people with advanced respiratory and cardiac diseases [8-10]. In a secondary analysis of clinical trials, improvement in breathlessness scores was independent of the underlying aetiology [11], suggesting that low-dose ER morphine may have a role in reducing PAH-associated breathlessness. However, only one participant with pulmonary hypertension as the primary cause of breathlessness was included in this analysis [11].

To date, no study has been conducted to investigate pharmacological agents for the symptomatic reduction of chronic breathlessness in PAH. Understanding the net effect (benefits and harms) of ER morphine for PAH-associated chronic breathlessness is crucial to inform care for these patients. This randomised controlled trial (RCT) aimed to investigate the effects and safety of low-dose, ER morphine for chronic breathlessness associated with

PAH. The null hypothesis was that there was no difference between placebo and ER morphine for the relief of chronic breathlessness in PAH.

Material and Methods

Study Design and Setting

This prospective, randomised, placebo-controlled, double-blind, cross-over study was conducted in two Australian health-care centres: Southern Adelaide Palliative Services (South Australia); and Austin Health (Victoria). Ethics approval was obtained from relevant Health Human Research Ethics Committees and the trial was registered (ACTRN12609000209291) before recruitment commenced. All participants gave informed written consent.

Participants

Participants were recruited from respiratory outpatient clinics and inpatients units. Adult participants were included if they had optimally-treated PAH as assessed by their treating respiratory physician. The diagnosis of PAH was based on the WHO classification [1]. Optimal treatment of PAH was assessed individually and included treatment with a dual endothelin antagonist and/or a phosphodiesterase inhibitor at the time the person was being assessed for participation in the trial. (Of note, the disease-modifying treatment of PAH has continued to evolve during the conduct of the study, and people were treated were given state-of-the-art treatment before entering the study. Patients were stabilised on the treatment regimen for several months and were still breathless.

Other inclusion criteria for this study were i) secondary heart failure class III or IV of the New York Heart Association functional classification [12] corresponding to marked limitation of physical activity due to breathlessness or breathlessness at rest, ii) calculated creatinine clearance of >10mmol/L, iii) optimised haemoglobin levels and iv) on stable medications over the previous seven days. Exclusion criteria included i) regular opioid medication, ii)

known hypersensitivity to morphine, iii) central hypoventilation syndrome, iv) use of monoamine oxidase inhibitors in the previous four weeks or proposed use during the study, v) Australian Karnofsky Modified Performance Status (AKPS) < 50 [13], vi) cognitive impairment (baseline mini-mental state examination < 24) [14], vii) uncontrolled nausea or vomiting, viii) gastrointestinal obstruction, ix) pregnancy or breastfeeding or x) history of opioid misuse.

Interventions

Each participant was randomised to one week of arm A or B, one week wash out and one week of the treatment they did not receive initially. The active arm consisted of once-daily morning 20mg Kapanol (ER morphine) capsule orally for seven consecutive days and two docusate with sennosides daily as prophylaxis against constipation. The control arm consisted of identical-looking placebo Kapanol and placebo docusate with sennosides. Participants were given additional open label docusate with sennosides to take as needed throughout the three week study.

Outcomes

The primary outcome was difference in mean breathlessness scores “right now” on the last three days of each treatment week collected in participant diaries using a 0-100 mm visual analogue scale (VAS). The last three days were chosen because morphine blood concentrations would be in steady state with this ER formulation. Differences in scores were calculated separately for morning and evening.

Secondary outcomes were between-treatment differences in:

- Mean scores of self-rated “average” and “worst” breathlessness in the previous 24 hours for the last three days of each treatment arm using the VAS;
- Self-rated quality of life measured using the McMaster Chronic Respiratory Questionnaire – Dyspnoea Sub-scale [15];

- Best self-rated modified Medical Research Council (mMRC) breathlessness score [16];
- Self-rated quality of sleep measured using a 4-item Likert scale and breathlessness' influence on sleep using dichotomous rating (yes/no);
- Respiratory rate, pulse oximetry and end-tidal carbon dioxide ($ETCO_2$);
- Frequency and severity of harms using the 5-point National Cancer Institute Common Terminology Criteria of Adverse Event reporting version 3.0 (NCI Criteria) [17]; and
- Participants' blinded preference for one of the study arms.

Randomisation

A computer number generator selected random permuted blocks of four with an equal allocation ratio. The Southern Adelaide Health Service (SAHS) clinical-trials pharmacist conducted the randomisation in a double-blind fashion (to participants and care providers). Clinical-trials pharmacists at each site had no contact with potential participants and dispensed study medications according to the randomisation schedule.

Medications for days 1 to 7 and for days 15 to 21 were provided separately. Two bottles were supplied to each participant at each stage: one containing the study drug (ER morphine or placebo) and a similar one containing the laxative (active drug or placebo).

Sample size considerations

The original sample-size calculation was estimated based on a previous study with similar design, in which 38 participants with different breathlessness aetiologies provided sufficient statistical power to detect a treatment effect of ER morphine on breathlessness [18]. This study analysis has shown the treatment – sequence interaction was non-significant (p=0.27), thus a linear mixed model was fitted with treatment (morphine vs. placebo), sequence

(morphine-placebo vs. placebo morphine), and time of day (am vs. pm) as independent variables. The residual within-subject variance was 82.8, and the estimated treatment effect was 3.7 mm, with a 95% confidence interval of (0.8 mm, 6.6 mm). In order to allow for sampling variability, the one-sided upper 95% confidence interval of the within-subject variance was calculated using the bootstrap (2000 replications) and it was found to be 112.0. This would provide a confidence interval for the treatment effect having width approximately 7 mm. Assuming that variability of breathlessness scores was broadly similar in the present population, it was estimated that 50 participants would provide 80% power to detect a 7 mm difference in the VAS with an α of 0.05, allowing for 20% drop-out rate as a clinically detectable difference [19].

Although this study did not reach target recruitment, it could still inform if it was appropriate to progress to a large phase III trial [20]. Importantly, a recent secondary analysis of three chronic breathlessness studies established the minimally clinically important difference (MCID) as 9 mm in the VAS for chronic breathlessness [19]. Consequently, the MCID was used in this study analysis instead of the 7 mm difference achieved in the initial sample size calculation. Given the difficulties with recruitment, we aimed to determine if ER morphine is likely to achieve a reduction of 9 mm in the VAS for breathlessness “right now” in both morning and evening, which is equivalent to an effect size of approximately 0.4 [19]. This would exclude an effect size of zero or less and inform if progression for a full-scale trial was adequate [20]. In a fully powered parallel-arm trial, a sample size of 186 ($1-\beta=0.8$, $\alpha=0.05$) would be required, which corresponds to approximately a sample size of 18 in a parallel-arm pilot study [20]. Assuming that there is less variability in breathlessness scores in a cross-over study, this current study sample (19 participants) would be adequate.

Statistical Methods

Because it was impossible to achieve the expected sample size, this study was analysed as an early phase study following the recommendations by Cocks and Torgerson [20]. SPSS

23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used to conduct descriptive statistics which evaluated the flow of participants through the study, the sample's baseline characteristics and breathlessness scores.

Given that this study was analysed as an early phase study, no formal statistical analysis was planned between groups. Descriptive statistics were used to report all outcome measures. Cohen's d effect sizes for the difference between the two treatments were calculated for the primary end-point and additional breathlessness measures. The 80% confidence intervals (CIs) of the effect sizes were examined to determine whether they excluded an effect size of zero or less (i.e. favouring placebo) which would suggest that a fully powered trial would be unlikely to detect a statistically or clinically significant difference (i.e. an advantage of 9 mm for the morphine treatment). This study is reported based on the CONSORT criteria [22].

Results

Recruitment and retention

Of 50 people assessed formally between March 2009 and December 2016, nine were already taking opioids, nine were unwilling to participate in this study and eight were not eligible for other reasons, such as advanced disease states or poor functional status. Twenty-three participants (46%) were eligible and randomised. Nineteen participants completed both treatment periods and were included in the analysis (Figure 1). Four participants withdrew, all while taking morphine (Table 1). Three participants stopped the study due to common harms attributable to morphine (nausea, vomiting, drowsiness). One participant stopped the study due to lethargy.

Study population

Participants (n=23) were mainly overweight or obese elderly women. Seven were on supplemental oxygen (Table 2). Most participants (84%) had idiopathic PAH. More than half of the participants (65%) were unable to carry on normal activity or do active work (AKPS ≤ 70).

Breathlessness

Considering the last three days of each treatment, mean breathlessness scores for breathlessness "right now" were higher with morphine compared with placebo both for morning [mean (M) ± standard deviation (SD) 31.7 ± 25 mm vs. 26.9 ± 22 mm] and evening (M±SD 33.5 ± 28 mm vs. 25.6 ± 21 mm). Similarly, breathlessness scores were higher with morphine for average breathlessness in the previous 24 hours (M±SD 43.7 ± 26 mm vs. 38.7 ± 24 mm) and worst breathlessness in the previous 24 hours (M±SD 55.6 ± 27 mm vs. 51.2 ± 23 mm; Table 3). Figure 2 shows the mean breathlessness scores for the seven days on each treatment.

Sleep and quality of life

Most participants stated either good or very good quality of sleep whether they were on ER morphine or placebo. Six participants felt they had better sleep quality while on ER morphine, three while on placebo and nine participants reported no difference between treatments. Only one participant in the morphine arm and two in the placebo arm stated that their sleep was disturbed by breathlessness.

Scores in the CRQ-SAS Dyspnoea Domain Score were similar between the two interventions (M±SD morphine 4.3 ± 1.8 vs. placebo 4.0 ± 1.5). Similarly, participants mMRC score on the last day of each treatment was not different between morphine [median (IQR) 2 (1 – 3)] and placebo [median (IQR) 2 (1 – 3)].

Harms

Respiratory rate in breaths per minute (bpm) was lower with ER morphine (M±SD 19.7 ± 5.3 bpm) compared with placebo (M±SD 21.4 ± 5.5 bpm) and $ETCO_2$ levels were higher with ER morphine (M±SD 30.8 ± 6.2 mmHg) compared with placebo (M±SD 28.5 ± 6.5 mmHg). Pulse oximetry was slightly lower with ER morphine (M±SD 92.6 ± 6.3% vs. 94.3 ± 2.9%; Table 4).

On the last day of each treatment, significantly more participants had nausea without alteration of the eating habits with morphine [(n=5 vs. n=1). Similarly, nine participants stated either occasional (n=6) or persistent (n=3) constipation with morphine while no participant stated constipation with placebo (n=0; Figure 3). Smaller differences were found for somnolence (ER morphine n=11 vs. placebo n=9). Confusion was slightly higher with placebo (ER morphine n=0 vs. placebo n=2). Vomiting was not reported with any of the treatments (Table 5).

Blinded participants' preference

Only six participants stated dissatisfaction with the study drug, three at the end of each active arm. Most participants reported being either satisfied or very satisfied with the study medication, whether that was morphine or placebo (n=12 vs. n=11 respectively).

Discussion

This first trial evaluating ER morphine for chronic breathlessness associated with PAH has shown that the direction and magnitude of effect favour placebo over ER morphine in every important outcome measure and that ER morphine generated consistently more harms. In addition, recruitment was very challenging.

Only 50 participants were formally assessed for this study during a period of more than seven years. Of those, only 23 were eligible to participate, which highlights that successful recruitment occurred in less than 50% of cases. Significantly, the research team recruiting for trial is one the world-leading teams in chronic breathlessness clinical trials research and has repeatedly recruited successfully to similar populations in other conditions that cause chronic breathlessness. Thus, it is important to reflect on reasons why the recruitment was not successful. Firstly, PAH is a very rare disease with a prevalence of 5-52 per million [23-25] and an estimated incidence of 1.1-2.4 cases per million per year [26]. Secondly, despite the broad eligibility criteria, recruitment was limited by participants' performance status and previous exposure to opioids. These are expected findings given this population's age and comorbidities. However, inclusion of these participants' data would disrupt the study analysis and, therefore, they were excluded.

Another key finding is that harms like nausea and constipation occurred more frequently with ER morphine than placebo at the end of the seven-day period. Interestingly, while constipation is a common long-term effect of opioids, nausea usually affects patients only

over the first few days and disappears with therapy continuation. The fact that nausea remains after seven days of ER morphine contrasts with other studies published so far [18,32] and suggests a detrimental effect of ER morphine in the population with PAH. In addition, all study withdrawals occurred during the ER morphine treatment period and were likely related to morphine.

Notably, there were no cases of major respiratory depression, which is in line with the results of a previous meta-analysis showing no evidence of clinically-significant respiratory depression in people with chronic breathlessness treated with regular, low-dose opioids [39].

An interesting finding is the population included in this study were mainly elderly women who were overweight or obese. Although this is not necessarily the typical PAH population, PAH is increasingly diagnosed in elderly people and the prevalence is higher in females [27, 28]. In addition, it is not clear whether this profile matches the clinical characteristics of people more affected by PAH-associated breathlessness. Nevertheless, these findings should be interpreted according to the population considered.

This study population was largely overweight, some of whom may have had obstructive sleep apnoea (OSA). OSA is frequently associated with PAH [33] and was not an exclusion criterion for this study. In people with OSA, morphine may potentially aggravate the condition by causing somnolence and depressing the chemoreceptor response to changes in arterial partial pressures of carbon dioxide, oxygen and variations in pH [34]. Indeed, for these participants, minor daily fluctuations in respiratory rate and $ETCO_2$ may reflect larger changes during sleep when the central drive is the rescue mechanism from periods of hypopnea/apnoea [35]. Thus, sleep disruption and sleep-disordered breathing may have been a confounder and limited the therapeutic efficacy of ER morphine on breathlessness despite high self-rated quality of sleep with ER morphine.

Additionally, a recent physiology study in people with OSA showed that 40mg of MS Contin did not reduce Borg-score ratings to single-breath inspiratory resistive loads compared to placebo [36]. While this experimental paradigm focused on the acute mechanical components of breathing discomfort, which may differ to the multidimensional clinical scenario of breathlessness, people with sleep-disordered breathing often have blunted respiratory sensation [37,38]. Thus, a lack of breathlessness improvement with morphine in people with sleep-disordered breathing may reflect a floor effect but further investigation is needed.

Although this study was unable to give a definitive answer on the efficacy of ER morphine to reduce PAH-associated chronic breathlessness, there was no favourable efficacy signal in the primary or secondary outcome measures. Importantly, all measures of breathlessness present negative effect sizes demonstrating that placebo performed consistently better than ER morphine for breathlessness. In fact, considering one of the primary outcomes for this study - breathlessness “right now” in the morning – a sample size of 71.516 participants would be required in a large scale trial to achieve a statistically and clinically significant difference between morphine and placebo in favour of morphine [20]. This contrasts with previously published studies of low-dose morphine for chronic breathlessness in the setting of other aetiologies where modest sample sizes generate clinically and statistically significant differences [10,18,29,30]. A recent meta-analysis revealed that opioids significantly improve the sensation of breathlessness in participants with severe chronic obstructive pulmonary disease (COPD) [10]. Similar results were found in heart failure [31,32]. A previous crossover RCT encompassing participants with differing breathlessness aetiologies showed that ER morphine was significantly more effective than placebo in safely reducing the intensity of breathlessness [18]. Interestingly, a *post hoc* pooled analysis of 213 people with chronic breathlessness has also shown that the underlying disease did not predict response to opioid therapy [11]. However, this analysis included a relatively low number of participants in each diagnostic group.

This study used ER morphine formulations because they are taken less often than immediate-release (IR) and therefore more convenient for patients. Morphine serum concentrations are more stable with ER formulations with lower maximum plasma concentrations (C_{max}) [40,41] and higher trough concentrations, which may be associated with fewer adverse events and more sustained benefits [42]. In the setting of pain, ER formulations have been shown to be more effective than IR formulations during initiation leading to more rapid analgesia with fewer harms [43].

However, harms leading to withdrawal in only one arm and ER morphine's inability to improve any measure of breathlessness in this study suggest that ER morphine may have little or no benefit in people with PAH. This opioid-unresponsive chronic breathlessness may be due to different peripheral and central mechanisms of the disease and will require further research to be fully understood.

The major research direction from this study is to understand the pathways for the perception of breathlessness in this group of patients given the very different results to all other studies conducted until now. This also requires careful review of data from studies to date that include heterogeneous aetiologies of breathlessness. These should be re-analysed with and without people with PAH to understand the net effect when those with PAH are excluded.

Conclusions

This first study of low-dose ER morphine for PAH-associated chronic breathlessness does not support the progression for a large phase III RCT given the rate of recruitment, lack of a signal for improvement with morphine and the potential for harms quantified. These findings also raise the hypothesis that PAH may be the first diagnostic group with a type of chronic

breathlessness unresponsive to morphine. Understanding the underlying mechanisms of PAH-associated chronic breathlessness and patients' response to morphine therapy is key future research.

Conflict of interests: DC is an unpaid advisory board member for Helsinn Pharmaceuticals. He is a paid consultant and receives payment for intellectual property with Mayne Pharma and is a consultant with Specialist Therapeutics Australia Pty. Ltd. DJE serves as a consultant for Bayer outside the topic of the current manuscript. DF, ME, DS and ZV disclose no competing interests relevant for this work.

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Tables

Table 1 - Reasons for withdrawal of 4 participants from the study

Participant	**Treatment on day of withdrawal**	**Reason for withdrawal**	**Attribution**
1	Morphine	Dizziness and vomiting	Probable
2	Morphine	Nausea and vomiting	Probable
3	Morphine	Drowsiness and confusion	Probable
4	Morphine	Lethargy and accelerated worsening of performance status	Possible

Table 2 - Screening characteristics of participants (n=23). Values are mean ± standard deviation or median (IQR) unless stated otherwise; BMI (Body mass index)– Kilograms (Kg)/Square meter(m2); AKPS – Australian Karnofsky Performance Status

Characteristics	
Age (years)	64 ± 11
Male Gender	n=7 (30%)
BMI (Kg/m^2)	30 ± 6.0
AKPS	70 (60 – 80)
90 – Able to carry on normal activity; minor signs or symptoms of disease	n=3 (13%)
80 – Normal activity with effort; some signs or symptoms of disease	n=5 (22%)
70 – Cares for self; unable to carry on normal activity or to do active work	n=9 (39%)
60 – Able to care for most needs; requires occasional assistance	n=4 (17%)
50 – Considerable assistance and frequent medical care required	n=2 (9%)
Diagnosis	
Idiopathic PAH	n=16 (84%)
PAH associated with connection tissue disease	n=3 (16%)
Proportion receiving supplemental oxygen	n=7 (30%)
Rate of oxygen delivery (l/min)	2.3 ± 0.95
Charlson Index - age adjusted	3.8 ± 1.7
Respiratory rate (breaths/min)	21 ± 5
Estimated arterial blood oxygen saturation via pulse oximetry (%)	95 (92-97)
End tidal CO_2 (mmHg)[a]	26 ± 7
Baseline breathlessness “right now” – morning (mm on VAS)	38 ± 23
Baseline breathlessness “right now” – evening (mm on VAS)	37 ± 22
Baseline average breathlessness previous 24 hours (mm on VAS)	44 ± 21
Baseline worst breathlessness previous 24 hours (mm on VAS)	61 ± 20
Baseline breathlessness score (CRQ-SAS Dyspnoea Domain Score)	3.6 ± 1.3

[a]*Measured with a portable capnography device during quiet breathing*

Table 3 – ER Morphine compared with placebo scores on the intensity of breathlessness in the last 3 days of each treatment period.

	Breathlessness Intensity (VAS score in mm)[a]						
	ER Morphine (n=19)			Placebo (n=19)			Effect size of the group difference
	Mean	SD	95% CIs	Mean	SD	95% CIs	
Right Now - Morning	31.7	25	20.7 to 42.7	26.9	22	17.0 to 36.8	-0.22 (-0.6 to 0.2)
Right Now - Evening	33.5	28	20.5 to 46.5	25.6	21	16.2 to 35.0	-0.33 (-0.8 to 0.1)
Average - previous 24h	43.7	26	31.7 to 55.7	38.7	24	27.7 to 49.7	-0.20 (-0.7 to 0.2)
Worst - previous 24h	55.6	27	43.6 to 67.6	51.2	23	41.2 to 61.2	-0.29 (-0.7 to 0.1)

[a]Breathlessness is measured with the visual analogue scale (VAS) for breathlessness, with zero as “no breathlessness” and 100 as “worst possible breathlessness”.

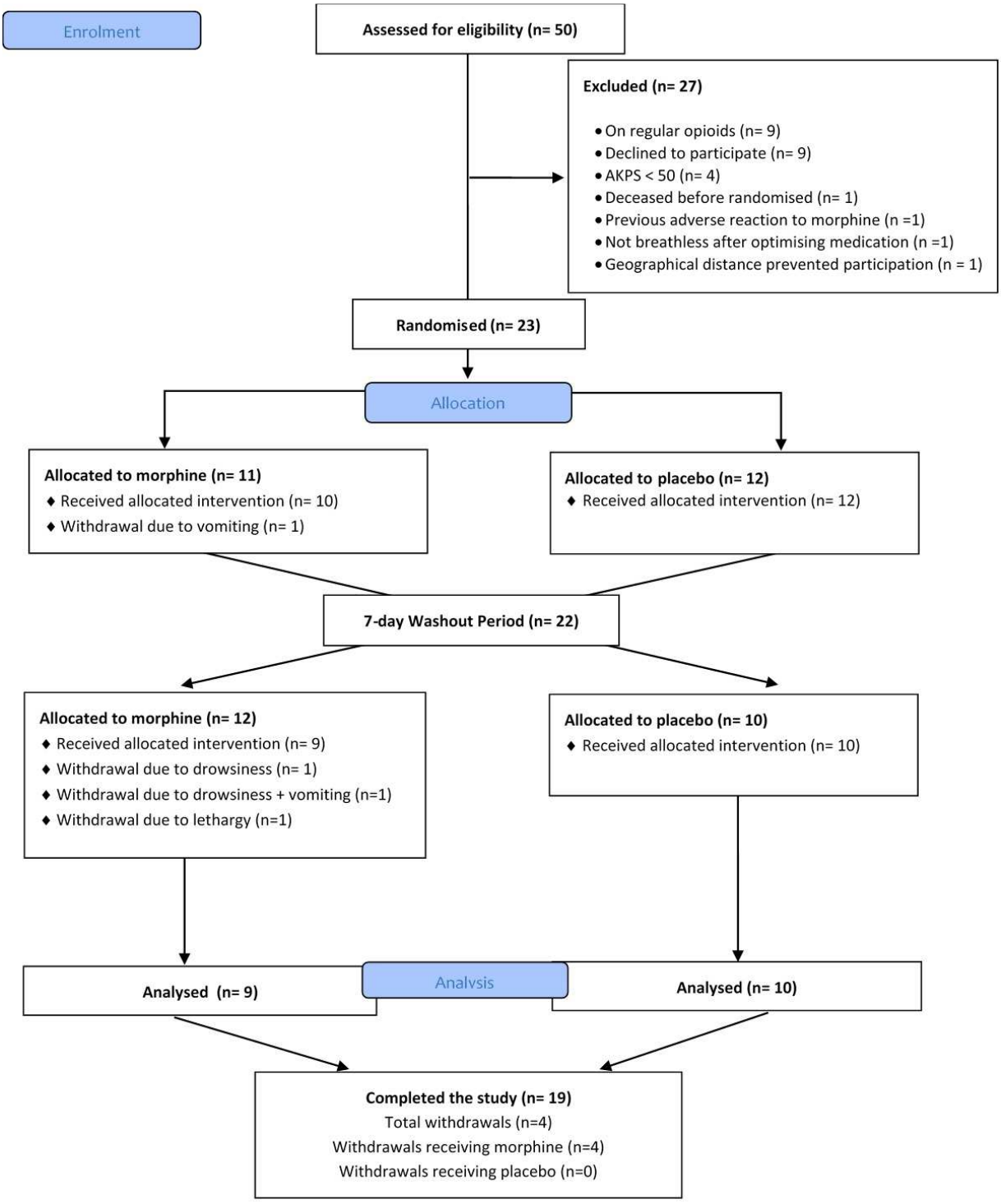
Table 4 – Differences in vital signs at the end of each treatment.

	ER Morphine		Placebo		Effect size of the group difference (95% CI)
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	
Respiratory rate (bpm)[a]	19.6 ± 5.3	20 (15-24)	21.4 ± 5.5	22 (17-24)	**1.08 (0.4 to 1.8)**
$ETCO_2$ (mmHg)	30.8 ± 6.2	31 (27-33)	28.5 ± 6.6	28 (26-33)	**-0.83 (-1.5 to -0.2)**
Pulse oximetry (%)	92.6 ± 6.3	94 (90-96)	94.3 ± 2.9	95 (93-96)	**0.50 (-0.2 to 1.1)**

[a]Breaths per minute

Table 5- Harms of morphine compared with placebo on day 7. Values for ER morphine and placebo are in absolute number of participants (percentages).

Harms (Day 7)	**ER Morphine (n=19)**	**Placebo (n=19)**
Nausea	**5 (36%)**	**1 (5%)**
Vomiting	0 (0%)	0 (0%)
Constipation	**9 (47%)**	**0 (0%)**
Confusion	0 (0%)	2 (9%)
Somnolence	11 (58%)	9 (41%)


Enrolment
Assessed for eligibility (n= 50)
Excluded (n= 27)
• On regular opioids (n= 9)
• Declined to participate (n= 9)
• AKPS < 50 (n= 4)
• Deceased before randomised (n= 1)
• Previous adverse reaction to morphine (n =1)
• Not breathless after optimising medication (n =1)
• Geographical distance prevented participation (n = 1)
Randomised (n= 23)
Allocation
Allocated to morphine (n= 11)
♦ Received allocated intervention (n= 10)
♦ Withdrawal due to vomiting (n= 1)
Allocated to placebo (n= 12)
♦ Received allocated intervention (n= 12)
7-day Washout Period (n= 22)
Allocated to morphine (n= 12)
♦ Received allocated intervention (n= 9)
♦ Withdrawal due to drowsiness (n= 1)
♦ Withdrawal due to drowsiness + vomiting (n=1)
♦ Withdrawal due to lethargy (n=1)
Allocated to placebo (n= 10)
♦ Received allocated intervention (n= 10)
Analysed (n= 9)
Analysis
Analysed (n= 10)
Completed the study (n= 19)
Total withdrawals (n=4)
Withdrawals receiving morphine (n=4)
Withdrawals receiving placebo (n=0)