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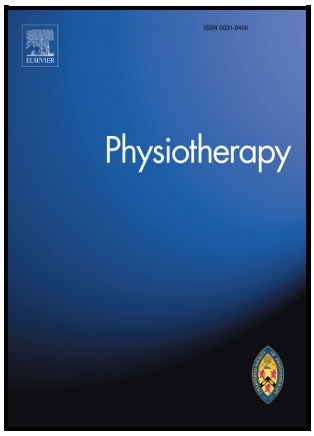
Non-Invasive Positive airway Pressure thErapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS): a pilot randomised control trial



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Title:

Non-Invasive Positive airway Pressure thErapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS): a pilot randomised control trial

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Ethical Approval: This study was approved by the Tasmanian Health Human Research Ethics Committee on 8th February 2017 (protocol reference H0016207) and the research was conducted according to the Declaration of Helsinki. All enrolled patients provided written informed consent.

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Abstract

Objectives: Postoperative pulmonary complications (PPC) are a common serious complication following upper abdominal surgery. Postoperatively, physiotherapy-led non-invasive ventilation (NIV) may be a promising method to reduce PPC incidence. The objectives of this pilot trial were to examine preliminary effectiveness, feasibility and safety of additional intermittent physiotherapy-led NIV compared to continuous high-flow nasal cannula oxygen therapy (HFNC) alone.

Design: Single-centre, assessor-blinded, parallel-group, pilot randomised control trial.

Setting: Primary-referral hospital in Australia.

Participants: 130 high-risk patients undergoing upper abdominal surgery.

Interventions: Continuous HFNC for 48-hours following surgical extubation, or HFNC plus five 30-minute physiotherapy-led NIV sessions.

Outcomes: PPC incidence, trial feasibility and safety.

Results: PPC incidence was similar between groups (HFNC alone 12/65 (18%) vs HFNC plus NIV 10/64 (16%) adjusted HR 0.95; 95% CI 0.40-2.29). Delivery of HFNC as per-protocol was achieved in 81% *(n=105)* of all participants. Physiotherapy-led NIV initiated within four-hours of surgical extubation was achieved in 81% (*n=52)* of intervention group participants, with a mean 4.2 (SD 1.3) total number of NIV sessions delivered in the first two postoperative days. NIV was delivered as per-protocol in 52% of this cohort. Two episodes of severe hypotension during NIV requiring medical intervention were reported.

Conclusion: Delivery of continuous HFNC was feasible. Delivery of NIV within four-hours of extubation was achieved and delivered safely with <1% adverse events. The planned NIV intervention of five sessions within two postoperative days was not feasible. The results of this pilot study have informed the decision not to proceed to a fully powered trial.

Clinical Trial Registration: Australian New Zealand Clinical Trials Registry, www.anzctr.org.au ACTRN12617000269336

Contribution of the Paper

- A protocol of continuous postoperative HFNC is feasible, well-tolerated and acceptable to high-risk adults following elective upper abdominal surgery.
- Prophylactic physiotherapy-led NIV within the early postoperative period is feasible in some cases. Physiotherapy-led NIV can be delivered safely to high-risk adults following elective upper abdominal surgery in the post-anaesthetic care unit, ICU and surgical ward setting.
- Delivery of a physiotherapy-led NIV protocol of five sessions over two postoperative days is not feasible to warrant progression to a future definitive trial.

Keywords: abdominal surgery, non-invasive ventilation, postoperative care, postoperative complications.

Introduction

Postoperative pulmonary complications (PPCs) are serious complications following upper abdominal surgery [1] and adversely influence mortality, morbidity and hospital costs [2-5]. The reported incidence of PPCs range from 3% to 42% [1-8], depending upon PPC definition and patient risk profile. The early postoperative period is associated with lung volume reduction and diaphragm dysfunction resulting in atelectasis, which if prolonged, can lead to hypoxemia, pneumonia and respiratory failure [9-11]. Strategies to optimise postoperative lung health and function are warranted [12].

Non-invasive ventilation (NIV) may prevent PPC following upper abdominal surgery [13-15]. Although recent guidelines support NIV use in the postoperative period [16], implementation of prophylactic NIV appears limited [15-17]. The reasons for which, are hypothesised to be perceived resource and safety concerns. No consensus exists regarding ideal duration of NIV sessions, with both prolonged continuous NIV [18] and intermittent sessions being as effective in minimising PPCs [14,19]. The resource burden with delivering prolonged NIV is considered high, with specialised environments and increased nurse-to-patient ratios required for continuous monitoring and safety [10]. As physiotherapists routinely provide postoperative care to abdominal surgery patients [20], such resources could be lessened, and therapy feasibility improved with physiotherapy-led, intermittent NIV. The safety and feasibility of physiotherapists providing NIV in the very early postoperative period is yet to be adequately reported.

Another therapy rapidly emerging as a possible method to enhance postoperative respiratory function is high-flow nasal cannula oxygen therapy (HFNC). Whilst the evidence for HFNC to prevent respiratory deterioration after cardiothoracic surgery is emerging [21,22], evidence for the benefit

after abdominal surgery is less clear [23]. Even so, HFNC use in postoperative care appears to be increasing [24].

Trials assessing HFNC alone versus HFNC co-administered with NIV in postoperative patients are recommended as a research priority [25]. Conducting pilot and feasibility studies prior to undertaking more extensive fully powered trials are considered an essential prerequisite to establish the viability of the proposed research study [26]. To assist planning a future definitive randomised control trial (RCT) to compare the use of additional intermittent physiotherapy-led NIV to continuous HFNC alone following elective high-risk upper abdominal surgery to reduce PPC incidence; this trial's objectives were to examine preliminary effectiveness, trial feasibility and adherence to the interventions, safety and cost-estimate data.

Methods

This was a single-centre, parallel-group, assessor-blinded, pilot RCT conducted in a regional, primary-referral, publicly funded hospital in Australia. Full protocol methodology is described elsewhere [27]. This study followed the Consolidated Standards of Reporting Trials for pilot and feasibility studies [28] and Template for Intervention Description and Replication [29] guidelines. This study was supported by the Clifford Craig Foundation, Launceston, Tasmania.

Participants

Patients eligible for inclusion were English-speaking adults attending preadmission clinic for elective open and/or hand-assisted laparoscopic upper abdominal surgery; and at high PPC risk defined in hierarchal order; (i) planned postsurgical admission to the intensive care unit (ICU)/high-dependency unit (HDU), or (ii) identified at high-risk using the Melbourne Risk Prediction Tool [7].

Patients were excluded if they had obstructive sleep apnoea requiring overnight continuous positive airway pressure (CPAP) or, extremely claustrophobic, a current inpatient for a separate care episode, expecting oesophageal or organ transplant surgery, or had contraindications to the first NIV application (Supplementary Table 1).

Patients listed for elective abdominal surgery are required to attend an outpatient preadmission assessment clinic, where patients are seen by a physiotherapist and receive PPC prevention education and trained in breathing exercises to start immediately upon waking from surgery [8]. Eligible patients were provided with a verbal explanation of the trial with written and pictorial information by the preoperative physiotherapist and invited to participate. Consenting patients provided written consent. On the day of each consenting patient's surgery, site investigators documented HFNC orders on their post-anaesthetic observation chart to instruct post-anaesthetic care unit (PACU) nursing staff to initiate HFNC following surgical extubation.

Randomisation

Consecutive eligible, consenting patients were randomly assigned by the lead or a site investigator in a 1:1 ratio post-surgery, using concealed opaque envelopes pre-prepared by a research assistant independent to the trial. Randomisation was stratified to post-surgical destination (ICU or WARD) and allocation sequence was generated by a web-based computer program. Patients were randomised to either control (HFNC for 48-hours post-surgical extubation) or intervention (control plus five, 30-minute, NIV sessions). The sample was divided into two blocks: 90 in the ICU block and 40 in the Ward block. The ratio of eligible ward participants was higher than expected and these envelopes were exhausted sooner than anticipated. Therefore, as pre-specified [27], the ICU block envelopes were used sequentially for nine ward participants.

Participants were withdrawn and excluded from analysis if they (i) required >48-hours of mechanical ventilation following surgery or (ii) withdrew consent.

Blinding

All preadmission and operating staff were unaware of group assignment. Outcome assessors and statisticians not involved in postoperative clinical management were blinded. All postoperative-care clinicians were aware of study-group assignment.

Interventions

Control Group

Participants randomised to the control group received HFNC continuously for 48-hours following extubation. Gas flow temperature was set pragmatically by ward staff and flow rate was set at 50 litres per minute (LPM), which could be reduced to 30LPM if higher flows were not tolerated. Fraction of inspired oxygen was titrated to achieve a saturation of peripheral oxygen ($Sp0_2$) between 92-96% [30] unless otherwise specified. All participants received preoperative physiotherapy [8]. Postoperatively, standardised physiotherapy-assisted ambulation was provided daily [31] until a threshold score was met [32]. No prophylactic respiratory physiotherapy was provided postoperatively. If a participant was diagnosed with a PPC, respiratory physiotherapy was provided at the discretion of the treating therapist. All other aspects of perioperative care were provided according to standard care.

Intervention Group

Intervention participants received care as per the control group plus an additional five postoperative physiotherapy-led 30-minute NIV sessions. The initial NIV session was to be delivered within four-hours of extubation, followed by twice daily sessions on postoperative days one and two. This service was provided in the PACU, ICU/HDU or surgical ward depending upon participant location. Prior to commencing NIV, participants were assessed for contraindications defined a priori [27] (Supplementary Table 1). A ResMed VPAP^{TM} machine (ResMed Ltd, Oxfordshire, UK) with a humidified circuit and standard facemask was used, with participants either sitting up in bed (head between 45–90 degrees) or in a chair. Expiratory positive airway pressure (EPAP) was set at $10cmH_20$ [10]. Inspiratory positive airway pressure (IPAP) was initially set at $15cmH_20$, then titrated to achieve tidal volumes of at least 6-8mls/kg. The difference between IPAP and EPAP was maintained at a minimum of $4cmH_20$ and the maximum total pressure provided was no greater than $25cmH_20$ [10]. Participants with a body mass index >30kg/m^2 had a starting EPAP of $12cmH_20$ and IPAP of $16cmH_20$.

If participants were unable to tolerate the set pressures, the following sequential modifications were made:

1. Reduce EPAP to 8cmH_20 (set minimum)
2. Reduce IPAP to 12cmH_20 (set minimum) in decrements of 1cmH_20

If participants were still unable to tolerate, then NIV was ceased.

Pressure rise time was set at the slowest speed (900ms) and the inspiratory trigger was set to the minimum value. Supplemental oxygen was titrated to achieve $Sp0_2$ 92-96% unless otherwise specified. Participants were continuously monitored and reassessed 30-minutes post NIV. Any reason resulting in early cessation or inability to provide NIV was documented. Sixteen physiotherapists with varying levels of experience (<1 to >10 years) provided the NIV intervention during work-hours Monday to Friday and within a four-hour ICU Saturday shift. Prior to the trial, all physiotherapists completed NIV training with the ICU Senior Physiotherapist.

Outcomes

One outcome measure was PPC occurrence within 14 postoperative days or hospital discharge, whichever occurred first. Participants were assessed daily until the seventh postoperative day using a standardised diagnostic screening tool [6-8,14,26,30] (Supplementary Table 2). From the seventh postoperative day, additional assessments were performed only if clinically suspected respiratory deterioration signs and symptoms were reported in the medical record.

Feasibility, protocol adherence, safety, and costs outcomes:

1) Patient consent and recruitment rates.
2) Protocol adherence of physiotherapy-led NIV. Successful adherence was set at ≤20% protocol deviations. This was assessed using:
    (i) Proportion of intervention participants who received NIV within four-hours of surgical extubation.
    (ii) Proportion of intervention participants who received five, 30-minute NIV sessions in the first two postoperative days.

(iii) Reasons for non-delivery/early cessation of NIV.

3) Protocol adherence of HFNC. Successful adherence was set at <20% protocol deviations. This was assessed using:

   (i) Proportion of participants who received HFNC for 48-continuous hours following surgical extubation.

   (ii) Time in minutes from extubation to commencement of HFNC.

   (iii) Reasons for non-delivery/early cessation of HFNC.

4) NIV Safety:

   (i) Major adverse events relating to NIV defined a prior (Supplementary Table 1).

   (ii) Transient physiological events during or immediately following NIV (Supplementary Table 1).

5) Estimated costs of HFNC and physiotherapy-led NIV service provision (Supplementary Table 3).

Further exploratory outcomes included; (i) pneumonia [33], (ii) systemic inflammatory response syndrome (SIRS), (iii) sepsis, (iv) post-surgical ICU and hospital length of stay (LOS), (v) unplanned ICU admission, (vi) reintubation rates, (vii) in-hospital, 30-day and 12-month mortality and (viii) 12-month health related quality of life (HRQoL) via the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) [34] (Supplementary Table 4).

Sample size

This pilot trial was funded to be conducted for a defined time period (18-months), not to a prespecified sample. Surgical throughput of eligible patients at our hospital predicted we would recruit a sample of 130 within this timeframe. A baseline PPC rate of 18% was anticipated based on our site's historical LIPPSMAck POP [8] trial data. Systematic reviews in NIV to prevent pneumonia following abdominal surgery report a relative risk reduction of approximately 60% compared to

standard oxygen therapy [13]. Using inference for proportion calculations for two independent samples; a total sample of 130 would detect a 50% relative risk reduction in PPC between groups (favouring the intervention group, alpha 0.05) with only 32% power. The sample size for this pilot study is designed to test the feasibility and safety of the intervention protocols with the aim to inform future definitive trials.

Statistical analysis

Baseline comparability and adjustment factors

Baseline characteristics between groups were compared to identify possible covariate imbalances, using general linear modelling or ordered logistic regression (where assumptions of linear regression were violated) for continuous variables; and Poisson regression for categorical variables.

Analysis of outcomes

Trial feasibility and protocol adherence outcomes were analysed using descriptive statistics. Time-to-event analysis was conducted to compare the risk of events in the treatment groups: PPC, pneumonia, SIRS, sepsis, mortality (in-hospital, 30-day and 12-month), ICU and total in-hospital post-surgical LOS. This comparison estimated hazards ratios using unadjusted and adjusted Cox proportional hazards regression (HR; 95% confidence intervals (CIs)). Times were censored by event occurrence, death or early discharge, or cessation of follow-up at 14-days (for PPC, pneumonia, SIRS and sepsis) or 30-days (for post-surgical LOS). For LOS measures, discharge alive from ICU or hospital was treated as the qualifying event, removing the ambiguity of early death and early hospital discharge being valued equally. Other events (ICU readmission, and re-intubation) were compared by estimation of incidence rate ratios using unadjusted and adjusted mixed effects negative binomial regression (IRR; 95% CIs). HRQoL (EQ-5D-5L Utility and visual analogue scale): Mean differences between groups (95% CIs) were estimated using unadjusted and adjusted mixed effects linear regression. Results of PPC and exploratory outcomes analyses were adjusted for covariates selected using backwards stepwise regression from specific baseline covariates considered *a priori* [27], plus covariates that showed baseline imbalance. As pre-specified [27], an intention-to-protocol sensitivity

analysis was also conducted. Analyses were conducted as intention-to-treat and performed using Stata MP2 V16.1 (StataCorp, College Station, Tx USA).

Results

From February 2017 to August 2018, 163 patients were assessed for eligibility with 130 meeting the inclusion criteria and randomly assigned to either HFNC alone (n=65; control) or HFNC plus NIV (n=65; intervention) (Figure 1). One participant was withdrawn from the intervention group leaving 129 included for primary analysis, 96% of participants were followed up to hospital discharge and 83% of participants were followed up at 12-months (Figure 1). Baseline characteristics are presented in Table 1. There were significant baseline imbalances between groups with respect to respiratory co-morbidity and functional co-morbidity index, which were adjusted for within the analysis. Whilst baseline differences between groups also exist for surgical categories, this did not reach significance. Full details of baseline characteristics, intraoperative and postoperative management are presented in Supplemental Table 5)

Outcomes

Postoperative pulmonary complications

A PPC was diagnosed in 22 of the 129 participants (17%). PPC rate was similar between groups. HFNC alone: 12/65, 18% vs HFNC plus NIV: 10/64, 16%; adjusted HR 0.95; 95% CI 0.40–2.29 (Supplementary Table 6). (Supplementary Figure 1 shows time to PPC between groups and Supplementary Table 7 details the per-protocol analyses).

Consent and recruitment feasibility

Consent rate was 96%, with one-to-two participants recruited per week.

Feasibility of intervention delivery

Protocol adherence of physiotherapy-led NIV

Of the 64 intervention participants, 52 (81%) had NIV delivered within four-hours of extubation and the mean (SD) total number of NIV sessions delivered was 4.2 (1.3). The planned physiotherapy-led NIV intervention was not successfully delivered, with only 33 (52%) participants receiving NIV as per-protocol. The main barriers to NIV delivery were physiotherapy service-related limitations with 12 (19%) participants not able to have at least one session of NIV due to unavailability of physiotherapy staff. Other reasons for non-delivery were medical advice to withhold therapy (n=10, 3%) and participant refusal (n=8, 3%) (Table 2).

Protocol adherence of HFNC therapy

The HFNC protocol was successful, with 81% (n=105) of participants receiving HFNC for 48-continuous hours. Mean time to HFNC delivery was 60.5 minutes (SD 49) from extubation with therapy commencement similar between groups (Table 3). The most common reasons for HFNC early cessation were participant's inability to tolerate/refusal (n=13, 10%) (Table 3). Nine protocol breaks to standardised postoperative physiotherapy were reported (Supplementary Table 8).

Safety

Two (<1%) major adverse events of severe hypotension occurred. One event required an increase in inotropes immediately after NIV commencement, 80-minutes after extubation. The second event required a small dose of inotropes to be initiated during NIV, 100-minutes after extubation. Transient physiological events occurred during or following 31 (12%) NIV sessions, without need for medical intervention (Table 2).

Costs

The HFNC plus NIV group utilised a higher amount of physiotherapy resources compared to the HFNC alone group; $405 (SD 64) v $123 (SD 2) (Supplementary Table 9).

Exploratory outcomes

Reintubation rates (3/64, 5% v 7/65, 11%; adjusted IIR 0.39; 95% CI 0.18-0.79) and unplanned/readmission to ICU (3/64, 5% v 6/65, 9%; adjusted IIR 0.43; 95% CI 0.19-0.93) were lower in the HFNC plus NIV group. There were no differences between groups in other exploratory outcomes (Supplementary Table 6).

Discussion

This pilot study evaluated preliminary effectiveness, feasibility and safety of intermittent physiotherapy-led NIV compared to the provision of HFNC alone to minimise PPCs after high-risk elective upper abdominal surgery. Incidence of PPC was similar between groups, costs (resources) for the HFNC plus NIV group were higher than for HFNC alone, and reintubation and ICU unplanned/readmission rates were higher in the HFNC alone group.

Patient consent, recruitment and follow-up rates were high, suggesting that the method of recruitment and experimental interventions are acceptable to patients. The use of HFNC in the PACU, ICU and ward setting were feasible with all participants commenced onto HFNC following surgery and 81% *(n=105)* receiving HFNC as per protocol. This suggests continuous prophylactic HFNC intervention is appropriate for future trial methodology. Results showed a mean time of one hour after extubation to HFNC commencement. Extubation onto HFNC in ICU is becoming increasingly common [35] however, extubation onto HFNC in the PACU is less reported and a new practice for our hospital specifically instigated for this trial. This may explain the time delay in post-extubation commencement of HFNC. To increase the success of the timing to immediate commencement of HFNC post-extubation, engagement and awareness of the intervention and trial protocol for all staff must be ensured.

Provision of physiotherapy-led NIV within four-hours of extubation had good treatment fidelity, with 81% *(n=52)* of participants receiving their first session as planned and a mean time to first NIV session of three-hours demonstrated. Following our previous work [14], a physiotherapy service was implemented within the PACU, which improved early NIV delivery. This study finds that physiotherapy-led NIV can be delivered safely in the PACU, ICU and ward settings with less than 1%

of adverse events. Participant adherence to the 30-minute NIV sessions was also shown to be adequate. This suggests physiotherapy-led intermittent NIV within four-hours after high-risk abdominal surgery is feasible and safe for full-scale trial progression. Whilst the adverse event rate was low, it is important to consider the severity of the safety events. Both adverse events occurred in the PACU, resulting in an increase in medical management (inotrope use). These medications are not able to be administered in a ward setting and if these events had occurred in a surgical ward, escalation of care and transfer to HDU/ICU may have been required. This should be considered when designing future trials investigating physiotherapy-led NIV.

The planned NIV intervention of five sessions within the first two postoperative days had low treatment fidelity and was not successful, with 52% *(n=33)* of participants receiving all five planned NIV sessions. This protocol was designed to match our previous study, whilst controlling for previously identified confounders which included non-standardised early mobilisation and postoperative chest physiotherapy [14]. The NIV intervention approach was based on knowledge that lung volumes reach their lowest within the first two postoperative days [19], with 85% of PPCs occurring within the first three postoperative days [3]. Our hospital provides a six-day physiotherapy service with on-call availability only on Sundays, therefore participants undergoing surgery on a Friday frequently missed their day two sessions. This was the main hindrance to NIV delivery. It could be suggested this may not be a barrier in larger, tertiary hospitals where a seven-day physiotherapy service is likely provided, or if physiotherapy staffing was increased. However, less than half of Australian hospitals are reported to provide a seven-day physiotherapy service [36] and costs required to increase weekend physiotherapy staffing may not be justified in relation to treatment efficacy.

Conducting pilot and feasibility studies to inform future trial design and viability of full trial progression in physiotherapy research and practice is important. Our results suggest a protocol of prophylactic physiotherapy-led NIV over two postoperative days should not be provided on a larger scale without major revision. In order to be successful, a multidisciplinary approach may need to embedded [19]. However, whilst NIV provided by nursing staff in ICU would be feasible due to both

prior training and one-to-one nursing staff ratios [37], pragmatically it is unlikely to be feasible for nursing staff to routinely provide and monitor NIV in the ward setting, where staffing ratios are considerably less and an increased demand on their resources/time is likely to be challenging. Alternatively, a different NIV dosage (duration and frequency) may need to be considered, however, the feasibility of a new NIV approach requires re-testing.

Since the completion of our study, a well-designed, adequately powered RCT; the PRISM trial (*n=4793*) recently demonstrated four-hours of prophylactic CPAP applied within four-hours of surgical extubation did not reduce 30-day pneumonia incidence, reintubation or mortality compared to standard care in patients following major abdominal surgery [38]. These results strongly suggest widespread adoption of postoperative CPAP to prevent PPC is not justified [38]. This study also found no difference in outcomes in a sub-group analysis of patients identified at high PPC risk (*n=992*). Similar to our findings, the authors highlighted the challenges of implementing routine prophylactic CPAP in the 'real-world' clinical setting [38]. In contrast to the PRISM trial, an earlier study by Squadrone and colleagues [18] in 2005, demonstrated significant improvements in pneumonia and reintubation rates with continuous CPAP in intermediate to high-risk abdominal surgery patients compared to standard care. Despite 16 years between these two studies, there are similarities regarding surgical procedures, anaesthetic duration, standard care of oxygen therapy and intervention approach. However, one key difference in study design, is participants in the earlier study had existing postoperative hypoxemia on trial entry [18]. This suggests a focused approach of 'rescue' CPAP in selected patients rather than prophylactic therapy to all patients, may be a more appropriate intervention for future trial protocols in this population. However, future research is needed to test and validate this theory.

Limitations

There are several significant limitations to this study, which include its single-centre design, an inability to blind clinicians delivering the intervention, significant baseline group differences despite concealed randomisation, and not being statistically powered to detect clinically relevant differences

in patient-centred outcomes. Despite these shortcomings, this study design allowed substantial testing of interventions prior to conducting full-scale trials and informed our decision not to proceed with a definitive trial.

Conclusion

Physiotherapy-led NIV was delivered safely, however, our NIV intervention protocol is not considered feasible to warrant progression to a future definitive trial. Further research into 'rescue' NIV in the high-risk abdominal surgery population may be more appropriate. The delivery of continuous prophylactic HFNC after high-risk abdominal surgery was shown to be feasible. Therefore, the HFNC protocol used in this pilot study could be used in future trials exploring the effectiveness of HFNC.

Conflict of Interest: The authors report no conflicts of interest.

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Figure Legend:

Figure 1 Flow of participants through trial. CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula oxygen therapy; NIV, non-invasive ventilation; OSA, obstructive sleep apnoea; PAC, preadmission clinic; UAS, upper abdominal surgery.

Fig 1

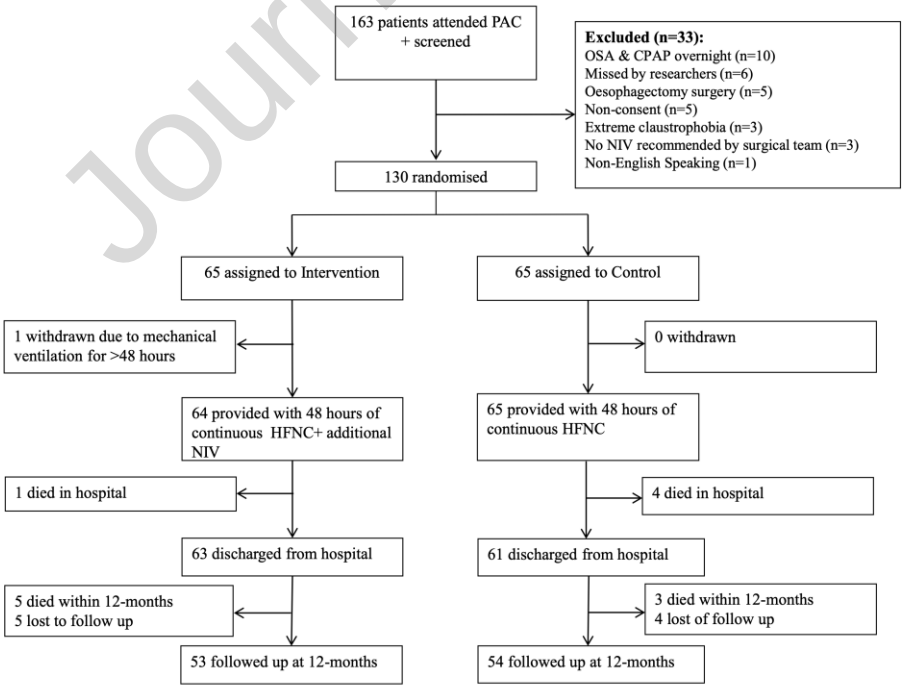

Table 1. Baseline Characteristics of Participants

	Control (HFNC alone) (n=65)	Intervention (HFNC + NIV) (n=64)
Age (year) mean (SD)	64 (12.0)	66 (13.1)
Sex, n (%)		
Male	39 (60)	45 (70)
Female	26 (40)	19 (30)
BMI (kg m^{-2}) mean (SD)	30 (7.0)	29 (5.8)
ASA physical health status, n (%)		
1 – 2	28 (43)	33 (52)
3 – 4	37 (57)	31 (48)
Comorbidities, n (%)		
Respiratory disease	30 (46)	15 (23)
Cancer	46 (71)	42 (66)
Cardiac disease	16 (25)	12 (19)
Diabetes	12 (18)	8 (13)
Functional Comorbidity Index (FCI), mean (SD)	3.4 (2.1)	2.5 (2.0)
Preoperative HRQoL, mean (SD)		
EQ-5D-5L Utility	0.8 (0.2)	0.8 (0.2)
EQ-5D-5L VAS	74 (17)	75 (17)
Smoking History, n (%)		
Non-Smoker	21 (32)	25 (39)
Current Smoker*	13 (20)	16 (25)
Ex-Smoker	31 (48)	23 (36)
Surgical category, n (%)		
Colorectal	25 (38)	31 (48)
Upper Gastrointestinal/Hepatobiliary	22 (34)	12 (19)
Urology	11 (17)	16 (25)
Other	7 (11)	5 (8)
Incision type, n (%)		
Midline laparotomy	42 (65)	45 (70)
Bilateral or unilateral subcostal	19 (29)	15 (23)
Abdominal + thoracotomy	0 (0)	1 (2)
Other upper abdominal incision	4 (6)	3 (5)

*Defined as still smoking or ceased <8 weeks

Abbreviations: ASA, American Society Anaesthesiologists; BMI, body mass index; HRQoL, health related quality of life; n, number of; SD, standard deviation; VAS, visual analogue scale

Table 2. Feasibility and Safety of Physiotherapy-Led NIV

NIV Protocol	**Intervention (HFNC + NIV) (n=64)**
NIV protocol adherence, n (%)	

Proportion of participants who received NIV as per protocol	33 (52)
Proportion of participants who received NIV within first 4 hours	52 (81)
Proportion of participants who received 5 NIV sessions in first 2 PODs*	41 (64)
Barriers to NIV delivery, n/320† (%)	
No barrier to NIV delivery	269 (84)
No physiotherapy service:	24 (8)
Out of hours POD 0	2 (1)
No Sunday service	22 (7)
Medical advice to withhold NIV	10 (3)
Participant refusal	8 (3)
Postoperative hypotension	3 (1)
Intubated and ventilated	3 (1)
Participant discharged	2 (1)
Postoperative agitation	1 (0.3)
Reasons for early cessation of NIV, n/269‡ (%)	
No early cessation required	252 (94)
Nausea and vomiting	8 (3)
Claustrophobia	6 (2)
Pain	2 (1)
Pressure discomfort despite pressure titration	1 (0.4)
No. of major adverse events, n (%)	
Severe hypotension requiring increase in medical management	2 (0.7)
No. of transient events, n (%)	
Hypotension, defined as a decrease in blood pressure >20mmHg	27 (10)
During or immediately after NIV	19 (7)
30-minutes post NIV	8 (3)
Vomiting	4 (1)
NIV delivery parameters, mean (SD)	
Time to first NIV session (hours)	3.2 (4.3)
No. of NIV applications delivered	4.2 (1.3)
Duration of POD 0 NIV (minutes)	29.1 (4.1)
Duration of POD 1 NIV (minutes)	
Session one	28.8 (4.6)
Session two	29.7 (2.5)
Duration of POD 2 NIV (minutes)	
Session one	29.0 (3.2)
Session two	29.8 (1.5)
IPAP delivered (cmH_20)	15.0 (1.1)
EPAP delivered (cmH_20)	10.2 (1.1)
Pressure titration required, n (%)	16 (6)

*Physiotherapy-led NIV delivered but not to protocol time frames of within four hours of extubation and 30-minute sessions

†Total number of NIV sessions planned to be delivered during the study period as per protocol (five per participant)

‡Total number of NIV sessions delivered during the study period

Abbreviations; EPAP, expiratory positive airway pressure; HFNC, high-flow nasal cannula oxygen therapy; IPAP, **inspiratory positive airway pressure; n, number; NIV, non-invasive ventilation; No, number of;** POD, postoperative day; **SD, standard deviation; cmH_20,** centimetre of water

Table 3. Feasibility of Postoperative HFNC

HFNC Protocol	All participants (n=129)	Control (HFNC alone) (n=65)	Intervention (HFNC + NIV) (n=64)
HFNC protocol adherence, n (%)			
Proportion of participants who received HFNC post-surgical extubation	129 (100)	65 (100)	64 (100)
Proportion of participants who received HFNC as per protocol	105 (81)	54 (83)	51 (80)
Barriers to HFNC delivery, n (%)	0 (0)	0 (0)	0 (0)
No. of participants who had early cessation of HFNC	24 (19)	11 (17)	13 (20)
Reasons for early HFNC cessation, n (%)			
Participant unable to tolerate HFNC	8 (6)	6 (9)	2 (3)
Participant refusal	5 (4)	2 (3)	3 (5)
Agitation	3 (2)	0 (0)	3 (5)
Accidental removal by nursing staff and/or participant	2 (2)	1 (2)	1 (2)
No reason specified	2 (2)	2 (3)	0 (0)
Medical advice to cease HFNC	1 (1)	0 (0)	1 (2)
Reintubation	1 (1)	0 (0)	1 (2)
Panic attack	1 (1)	0 (0)	1 (2)
Discharged home	1 (1)	0 (0)	1 (2)
HFNC delivery parameters, mean (SD)			
Time from extubation to HFNC commencement (mins)	60.5 (49)	57.5 (51)	63.5 (47)
Duration of HFNC (hours) in the first 48 hours	44.6 (9.2)	44.9 (9.5)	44.3 (9.0)
Flow rate provided (LPM)	46.1 (10.3)	46.2 (10.5)	45.9 (10.1)
$Fi0_2$ provided (%)	27.7 (8.7)	28.3 (9.1)	27.0 (8.2)

Abbreviations; HFNC, high-flow nasal cannula oxygen therapy; $Fi0_2$, fraction of inspired oxygen; LPM, litres per minute; mins, minutes; n, number; NIV, non-invasive ventilation; SD, standard deviation