Postoperative continuous positive airway pressure to prevent pneumonia, re-intubation, and death after major abdominal surgery (PRISM): a multicentre, open-label, randomised, phase 3 trial

*PRISM trial group**

Summary

Background Respiratory complications are an important cause of postoperative morbidity. We aimed to investigate whether continuous positive airway pressure (CPAP) administered immediately after major abdominal surgery could prevent postoperative morbidity.

Methods PRISM was an open-label, randomised, phase 3 trial done at 70 hospitals across six countries. Patients aged 50 years or older who were undergoing elective major open abdominal surgery were randomly assigned (1:1) to receive CPAP within 4 h of the end of surgery or usual postoperative care. Patients were randomly assigned using a computer-generated minimisation algorithm with inbuilt concealment. The primary outcome was a composite of pneumonia, endotracheal re-intubation, or death within 30 days after randomisation, assessed in the intention-to-treat population. Safety was assessed in all patients who received CPAP. The trial is registered with the ISRCTN registry, ISRCTN56012545.

Findings Between Feb 8, 2016, and Nov 11, 2019, 4806 patients were randomly assigned (2405 to the CPAP group and 2401 to the usual care group), of whom 4793 were included in the primary analysis (2396 in the CPAP group and 2397 in the usual care group). 195 (8·1%) of 2396 patients in the CPAP group and 197 (8·2%) of 2397 patients in the usual care group met the composite primary outcome (adjusted odds ratio 1·01 [95% CI 0·81–1·24]; p=0·95). 200 (8·9%) of 2241 patients in the CPAP group had adverse events. The most common adverse events were claustrophobia (78 [3·5%] of 2241 patients), oronasal dryness (43 [1·9%]), excessive air leak (36 [1·6%]), vomiting (26 [1·2%]), and pain (24 [1·1%]). There were two serious adverse events: one patient had significant hearing loss and one patient had obstruction of their venous catheter caused by a CPAP hood, which resulted in transient haemodynamic instability.

Interpretation In this large clinical effectiveness trial, CPAP did not reduce the incidence of pneumonia, endotracheal re-intubation, or death after major abdominal surgery. Although CPAP has an important role in the treatment of respiratory failure after surgery, routine use of prophylactic post-operative CPAP is not recommended.

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See Online for appendix

Introduction

One in six patients undergoing major surgery have a postoperative complication before hospital discharge, including respiratory complications and infections, which are strongly associated with reduced long-term survival.[1–4] Since more than 310 million patients have major surgery worldwide each year,[5] many of whom are older (aged >75 years) with clinically significant comorbidities, poor postoperative outcomes are an important focus for society due the potentially large negative consequences they can have.[6,7] One of the most frequent and serious complications of major surgery is pneumonia, which can lead to respiratory failure requiring mechanical ventilation and, in some cases, death.[8] The risk of postoperative respiratory complications might be increased by the residual effects of anaesthesia and surgery, including postoperative pain, depression of respiratory drive by narcotic medication, neuromuscular blockade, pulmonary atelectasis, and pulmonary collapse.[9,10] These factors are particularly important after major abdominal surgery because surgical manipulation within the abdomen and postoperative pain can further impair respiratory function, reducing natural protective mechanisms such as coughing, and worsening pulmonary atelectasis.

Continuous positive airway pressure (CPAP) is a safe and reliable method of non-invasive respiratory support, which is widely available in the majority of hospitals around the world.[11–14] CPAP can be delivered by facemask, nasal mask, or hood device, and applies a continuous positive pressure to the upper airways for the entire

Research in context

Evidence before this study

The Cochrane Collaboration published a systematic review and meta-analysis that included all randomised trials published up to Sept 15, 2013, in which CPAP was compared with standard care for prevention of postoperative mortality and adverse events following major abdominal surgery. From 5236 studies identified in the search, ten small clinical trials (n=709) of postoperative continuous positive airway pressure (CPAP) delivered through a mask or hood were eligible for inclusion in the meta-analysis. Most trials were done at a single centre and the risk of bias was high. In five trials (n=563), CPAP reduced the incidence of pneumonia (risk ratio 0·43 [95% CI 0·21–0·84]; I^2=0%). In two trials (n=411), CPAP reduced the incidence of re-intubation, a marker of severe respiratory failure (RR 0·14 [0·03–0·56]; I^2=0%). In two trials (n=413), no clear difference was identified in all-cause mortality between patients in CPAP and control groups (RR 1·28 [0·35–4·66]; I^2=75%). In six trials that reported pulmonary atelectasis (n=249), CPAP reduced the incidence of atelectasis (RR 0·62 [0·45–0·86]; I^2=61%). Most of the existing evidence to support CPAP is derived from small single centre trials. At present, routine postoperative CPAP has not been adopted as standard clinical practice in any country.

Added value of this study

PRISM was a pragmatic, open-label, randomised clinical trial of preventative CPAP after major open abdominal surgery in 70 hospitals in six countries. In a real-world sample of patients, we found that CPAP did not reduce the incidence of pneumonia, re-intubation, or death within 30 days after surgery, or mortality within 1 year after surgery. This trial substantially increases the quality of the available evidence that anaesthetists, surgeons, and critical care physicians can use to inform their clinical practice.

Implications of all the available evidence

The current body of evidence does not support the routine use of CPAP as a preventative intervention to reduce the incidence pneumonia, endotracheal re-intubation, or death after major open abdominal surgery.

respiratory cycle. Most evidence is derived from small, single-centre trials, and suggests that preventative CPAP early after major surgery might prevent subsequent respiratory complications, perhaps by reducing the incidence of atelectasis and pulmonary collapse.[15–17] CPAP might also improve outcomes in patients who develop respiratory failure after major surgery.[16,17] However, to date, this treatment approach has not been adopted in routine clinical practice in any country.

We aimed to investigate whether CPAP administered within 4 h of major open abdominal surgery would reduce the incidence of pneumonia, endotracheal re-intubation, and death within 30 days after randomisation, compared with usual postoperative care.

Methods

Study design and participants

PRISM was an open-label, randomised, phase 3 trial done at 70 hospitals in Italy, Norway, South Africa, Spain, Sweden, and the UK. Eligible patients were aged 50 years or older who were undergoing elective major intra-peritoneal surgery using an open surgical technique (ie, the incision was larger than that required to remove the surgical specimen). Patients were excluded if they refused or were unable to provide written informed consent; had an anticipated requirement for invasive or non-invasive mechanical ventilation for at least 4 h after surgery as part of routine care; were pregnant; had previously been enrolled in the PRISM trial; or had previously participated in another clinical trial of a treatment with a similar biological mechanism or associated primary outcome.[18] Patients were screened and approached by a local investigator, in most cases, before the day of surgery. A detailed and standardised dataset was collected before, during, and after surgery using an online database.

The trial was overseen by a trial steering committee with an independent chair and two additional independent members (appendix p 2). Safety was monitored by an independent data monitoring and ethics committee (DMEC), who reported to the trial steering committee. Day-to-day management of the trial was done by the chief investigators and their support staff. The trial was done in accordance with the principles of the Declaration of Helsinki and the Research Governance Framework.[19,20] The trial protocol (appendix p 62) was approved by a research ethics committee in the UK (15/LO/1595) and by the local ethics committees or institutional review boards in other participating countries, and has been published previously.[18]

Randomisation and masking

Patients were randomly assigned (1:1) to receive the CPAP intervention or usual care using a computer-generated dynamic procedure with the use of minimisation to balance trial group assignments according to country, planned surgical procedure category, and planned use of epidural anaesthesia. The surgical procedure categories were resection of colon, rectum or small bowel; resection of liver, pancreas, or gall bladder; resection of stomach (non-obesity surgery); resection of oesophagus (non-obesity surgery); obesity surgery; vascular surgery; or other intra-peritoneal surgery. The randomisation system was accessed by investigators via a secure website, which concealed the allocation sequence. Each patient was allocated with

80% probability to the group that minimised between-group differences in these factors among all participating patients recruited to the trial to date, and to the alternative group with 20% probability. It was not possible to mask patients or clinicians delivering the intervention to the study group allocation; however, investigators collecting follow-up data were masked to group allocation. To quantify the degree of blinding, each investigator collecting primary outcome data completed a self-assessment of blinding.

Procedures

Patients were assigned to receive CPAP for at least 4 h within 4 h of the end of surgery or to usual postoperative care. The duration of CPAP was chosen through expert consensus, balancing the evidence from previous research against the need to test an intervention that was feasible for routine use in high-volume post-anaesthetic recovery units with variable skillsets among nursing staff. The airway pressure was started at 5 cm H_2O and then increased to a maximum of 10 cm H_2O at the discretion of the treating clinician. The fraction of inspired oxygen was at the discretion of the treating clinician. Patients in the usual care group received standard care for the participating hospital, consisting of supplemental oxygen therapy, without supplementary respiratory support unless clinically indicated.

Outcomes

The primary outcome was a composite of pneumonia, endotracheal re-intubation, or death within 30 days of randomisation. Pneumonia was defined according to the US Centres for Disease Control Definition, comprising three criteria.[21] First, patients had to have two or more serial chest radiographs with at least one of the following features: new or progressive and persistent infiltrate; consolidation; or cavitation. For patients with no underlying pulmonary or cardiac disease, one chest radiograph was considered sufficient. Second, patients had to have one of the following: fever (>38°C) with no other recognised cause; leukopenia ($<4\times10^9$/L), or leukocytosis ($>12\times10^9$/L); or for adults aged 70 years old and older, altered mental status with no other cause. Third, patients had to have at least two of the following: new onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements; new onset or worsening cough or dyspnea, or tachypnea; rales or bronchial breath sounds; or worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand). Endotracheal re-intubation was defined as re-insertion of an endotracheal tube after the patient had been extubated following the completion of the index surgical procedure. Endotracheal extubation was defined as an intentional clinical decision to remove an endotracheal tube, which did not include accidental or inadvertent removal of an endotracheal tube. Re-intubation did not include intubation for anaesthesia due to subsequent surgical procedures within the follow-up period.

Secondary outcomes were pneumonia within 30 days of randomisation, endotracheal re-intubation within 30 days of randomisation, death within 30 days of randomisation, postoperative infection within 30 days of randomisation, mechanical ventilation (invasive or non-invasive) within 30 days of randomisation, and all-cause mortality within 1 year of randomisation. The secondary outcome of quality-adjusted life-years 1 year after randomisation will be reported elsewhere. Postoperative infections were assessed according to prespecified and standardised definitions (appendix p 33). Additional outcomes were readmission to hospital within 30 days of randomisation, days in critical care (both high dependency and intensive care), and duration of primary hospital stay. Adverse events were reported in the CPAP group only, since we were primarily concerned with issues that affect the safety and effectiveness of CPAP delivery, and only where considered to be at least possibly associated with the trial intervention.

Statistical analysis

We determined that a sample of 4800 patients would provide 90% power to detect a reduction from 11·7% to 8·8% in the 30-day composite outcome of pneumonia, endotracheal re-intubation, or death, at an α level of 0·05. This calculation allowed for a rate of withdrawal and loss to follow-up of 4%.[18]

Statistical analysis was done in accordance with a prespecified statistical analysis plan (appendix p 63) along with a schedule of amendments. STATA (version 14.0) was used for data analysis. We used an intention-to-treat approach: all patients with a recorded primary outcome were included in the analysis according to the treatment to which they were allocated. Patients with missing outcome data were excluded from the analysis.[22] The magnitude of the treatment effect estimate was reported as an adjusted odds ratio with 95% CIs for primary and secondary outcomes. All p values were two-sided with a significance level of 5%. Summary statistics are presented as mean (SD), median (IQR), or number (%) for each treatment group. Baseline demographic and clinical data are summarised.

The primary analysis was presented as a mixed-effect logistic regression model, with a random intercept for centre.[23] We adjusted the model for the minimisation variables as fixed factors: country, planned use of epidural, and planned surgical category,[24] and for the following prespecified baseline covariates: age, sex, presence of comorbid disease, current smoker, and American Society of Anesthesiologists (ASA) Physical Status Classification grade.[25] Missing data for baseline covariates were handled using mean imputation for age, and a missing indicator was added for missing data for categorical variables (sex, comorbid disease, smoking

status, and ASA grade).[26] Secondary outcomes were analysed according to the intention-to-treat principle, with the exception that we only adjusted for minimisation variables, excluding country, to avoid over stratification, since the expected event rate for these outcomes was lower. We did a time to event analysis for the primary and secondary outcomes on a complete case basis and presented these as Kaplan-Meier plots. Safety was analysed in all patients assigned to the CPAP group who received CPAP.

We did a prespecified subgroup analysis for the primary outcome by surgical procedure category (lower gastrointestinal, hepatobiliary, upper gastrointestinal) and other (obesity surgery, vascular surgery, or other intra-peritoneal surgery). For the subgroup analysis we used the same analysis model as the primary analysis, including an interaction term between planned surgical procedure and treatment group. Since this was a pragmatic trial of a real-world intervention, it was plausible that some patients might not have received the treatment they were allocated. To investigate the effect of the intervention the patients received, we did a prespecified per-protocol analysis using inverse probability-weighting for the primary outcome and the following secondary outcomes: pneumonia within 30 days of randomisation, endotracheal re-intubation within 30 days of randomisation, and death within 30 days of randomisation. Since post-randomisation exclusions can cause bias, we used weighting to account for baseline risk factors that we expected to be joint determinants of adherence and the outcome (appendix p 63). This analysis estimated the effect of treatment if all participants in the group had started CPAP as intended by using a hypothetical strategy to account for non-adherence.[27] We used the same analysis models as used for the primary and secondary outcomes.

Additionally, we did a post-hoc per-protocol analysis using inverse probability-weighting with a slight variation whereby we defined patients in the intervention group who did not receive any CPAP due to being too unwell or remained intubated as having received the intervention. To assess whether the results were consistent for patients at high-risk of postoperative pulmonary complications, we did a post-hoc subgroup analysis of patients with a preoperative Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score[28] greater than 45 (indicating high-risk for pulmonary complications).

To better understand the delivery of the trial intervention, we embedded a prospective mixed methods process evaluation within the PRISM trial. This combined data from ethnographic case studies in four hospitals (observations in areas where the intervention was delivered, staff focus groups [n=29 staff members], patient telephone interviews [n=8]), and patient data. Principal investigators completed a 16-question trial exit questionnaire (54 of 70 hospitals responded). Case-study hospitals were selected according to size, volume of patients recruited, and intervention compliance. Thematic analysis was used to generate emergent themes from the qualitative data and descriptive statistics were used to analyse protocol deviations and questionnaire responses. All data were collected by an independent researcher and analysed before the main trial analysis. This study is registered with the ISRCTN registry, ISRCTN56012545.

For the **prospective mixed methods process evaluation** see https://qmro.qmul.ac.uk/xmlui/handle/123456789/72273

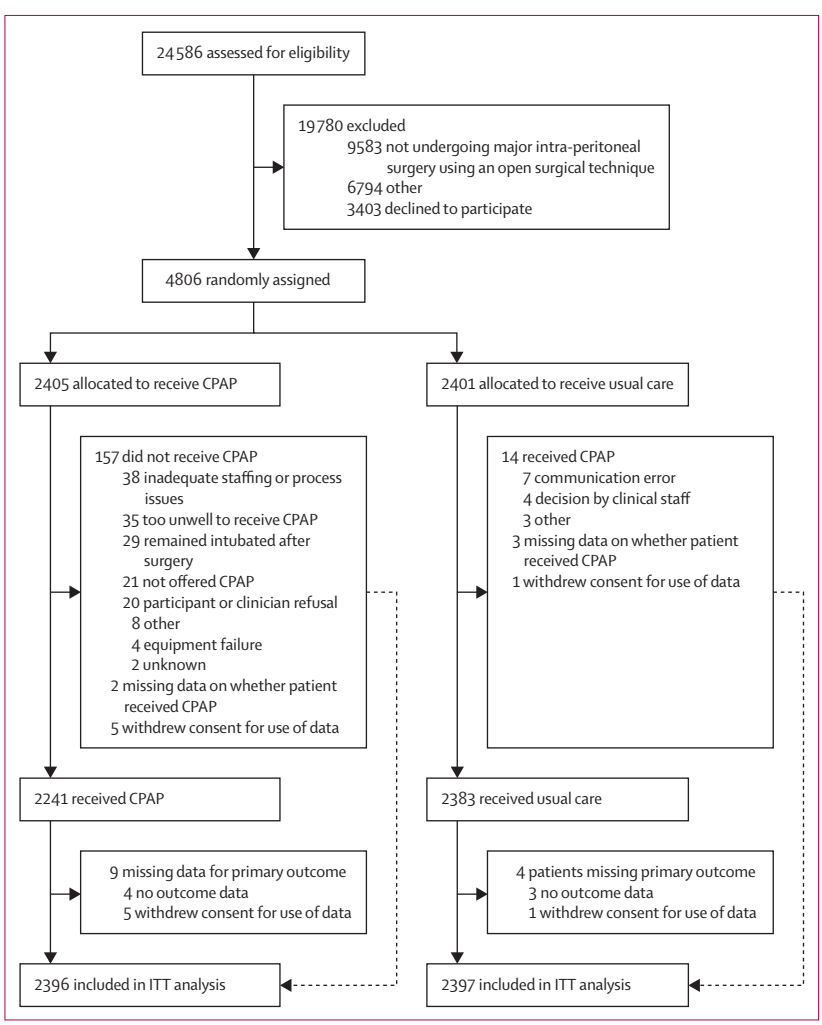

Figure 1: **Trial profile**
CPAP=continuous positive airway pressure. ITT=intention-to-treat.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the Article, or the decision to publish the study.

Results

Between Feb 8, 2016, and Nov 11, 2019, 24 586 patients were assessed for eligibility, of whom 4806 were enrolled (figure 1) across 70 hospitals in the UK (n=42), Italy (n=17), Spain (n=3), Norway (n=3), South Africa (n=3), and

	Usual care	CPAP
Sex		
Men	1278/2400 (53·3%)	1292/2400 (53·8%)
Women	1122/2400 (46·8%)	1108/2400 (46·2%)
Age, years		
Patients with available data, n	2400	2400
Mean (SD)	67·9 (9·2)	67·8 (9·2)
Median (IQR)	68·6 (60·6–74·6)	68·1 (60·6–74·5)
Current smoker	318/2395 (13·3%)	338/2397 (14·1%)
American Society of Anaesthesiology physical status classification*		
Grade 1	126/2387 (5·3%)	129/2390 (5·4%)
Grade 2	1284/2387 (53·8%)	1298/2390 (54·3%)
Grade 3	955/2387 (40·0%)	932/2390 (39·0%)
Grade 4	21/2387 (<1%)	31/2390 (1·3%)
Grade 5	1/2387 (<1%)	0
Chronic comorbid disease†		
Chronic obstructive pulmonary disease	228/2395 (9·5%)	233/2398 (9·7%)
Asthma	185/2395 (7·7%)	213/2398 (8·9%)
Interstitial lung disease or pulmonary fibrosis	22/2395 (<1%)	26/2398 (1·1%)
Bronchiectasis	11/2395 (<1%)	19/2398 (<1%)
Ischaemic heart disease	235/2395 (9·8%)	230/2398 (9·6%)
Diabetes mellitus	437/2395 (18·2%)	395/2398 (16·5%)
Heart failure	60/2395 (2·5%)	64/2398 (2·7%)
Liver cirrhosis	82/2395 (3·4%)	77/2398 (3·2%)
Active cancer	1924/2395 (80·3%)	1926/2398 (80·3%)
Previous stroke or transient ischaemic attack	129/2395 (5·4%)	105/2398 (4·4%)
Primary respiratory infection within the previous month	50/2395 (2·1%)	52/2397 (2·2%)
HIV infection	19/2394 (<1%)	23/2398 (<1%)
(Table 1 continues in next column)		
(Continued from previous column)		
Planned surgical procedure		
Resection of colon, rectum, or small bowel	924/2400 (38·5%)	922/2400 (38·4%)
Resection of liver, pancreas, or gall bladder	630/2400 (26·3%)	631/2400 (26·3%)
Resection of stomach (non-obesity surgery)	68/2400 (2·8%)	67/2400 (2·8%)
Obesity surgery	1/2400 (<1%)	0
Vascular procedure	69/2400 (2·9%)	71/2400 (3·0%)
Other intraperitoneal surgery	708/2400 (29·5%)	706/2400 (29·4%)
Resection of oesophagus (non-obesity surgery)	0	3/2400 (<1%)
Planned use of epidural anaesthesia	1134/2400 (47·3%)	1131/2400 (47·1%)
Country		
Italy	574/2400 (23·9%)	573/2400 (23·9%)
Spain	37/2400 (1·5%)	36/2400 (1·5%)
Sweden	63/2400 (2·6%)	65/2400 (2·7%)
UK	1421/2400 (59·2%)	1421/2400 (59·2%)
South Africa	99/2400 (4·1%)	99/2400 (4·1%)
Norway	206/2400 (8·6%)	206/2400 (8·6%)
ARISCAT score‡		
Patients with available data, n	2352	2363
Mean (SD)	40·8 (9·3)	41·1 (9·0)

Denominators for summary measures vary due to missing data and patient withdrawal. Data are n/N (%), unless otherwise stated. CPAP=continuous positive airway pressure. ARISCAT=Assess Respiratory Risk in Surgical Patients in Catalonia. A full summary of baseline characteristics and number of patients with available data used for each summary measure are provided in the appendix (p 12). *Grades are defined as follows: 1, a healthy patient; 2, a patient with mild systemic disease that does not limit physical activity; 3, a patient with severe systemic disease that limits physical activity; 4, a patient with severe systemic disease that is a constant threat to life; 5, a moribund patient who is not expected to survive without the operation. †Some patients had more than one chronic comorbid disease. ‡Components of the ARISCAT score are provided in the appendix (p 30).

Table 1: **Baseline patient characteristics**

Sweden (n=2). Patient recruitment was stopped once the target sample size had been reached. Of the 4806 participants who were enrolled, 2405 were randomly assigned to the CPAP group and 2401 patients were assigned to the usual care group. Seven (0·1%) of 4806 patients were missing data for the primary outcome and six (0·1%) of 4806 patients withdrew consent, thus, 2396 (99·6%) of 2405 patients in the CPAP group and 2397 (99·8%) of 2401 patients in the usual care group were included in the primary intention-to-treat analysis (figure 1). Four patients (<0·1%) withdrew from the trial but gave permission to include their data and were included in the primary analysis. The mean age of participants was 67·8 years (SD 9·2) and 2230 (46·4%) of 4800 patients were women (table 1; appendix p 12). Patient care is described in table 2 and the appendix (p 14).

2241 (93·5%) of 2398 patients allocated to the intervention group received CPAP (appendix p 16). The mean duration of CPAP was 194·2 min (SD 97·4) and the median duration was 240 min (IQR 149–240). 1564 (69·8%) of 2241 patients received CPAP using a facemask, 568 (25·3%) received CPAP via a hood device, and 28 (1·2%) received CPAP using a nasal mask; CPAP delivery method was not recorded for 81 (3·6%) of 2241 patients. The median interval between the end of surgery and the start of CPAP was 90 min (IQR 45–165). 157 (6·5%) of 2398 patients allocated to the CPAP group did not receive CPAP and 686 (30·6%) of the 2241 patients who did receive CPAP, received the intervention for less than 4 h (appendix pp 16–17).

At 30 days after randomisation, no significant differences were identified in the incidence of the composite primary outcome of pneumonia, endotracheal re-intubation, or death: 195 (8·1%) of 2396 patients in the CPAP group and

	Usual care	CPAP
Open surgical technique used during surgery	2389/2397 (99·7%)	2387/2398 (99·5%)
Anaesthetic technique		
General anaesthesia	2394/2397 (99·9%)	2394/2398 (99·8%)
Epidural anaesthesia	1053/2394 (44·0%)	1035/2398 (43·2%)
Spinal anaesthesia	436/2394 (18·2%)	456/2397 (19·0%)
Endotracheal tube inserted	2346/2394 (98·0%)	2343/2397 (97·7%)
Mechanical ventilation during surgery		
Recruitment manoeuvre	430/2340 (18·4%)	446/2350 (19·0%)
Mechanical ventilation	2381/2393 (99·5%)	2388/2396 (99·7%)
Intravenous fluids during surgery (excluding blood products), mL*		
Patients with available data, n	2394	2392
Mean (SD)	2872·1 (1659·4)	2871·9 (1536·4)
Total volume of blood products administered, mL†		
Patients with available data, n	2393	2391
Mean (SD)	120·0 (465·8)	101·4 (385·1)
Planned level of care on the first night after surgery		
Critical care unit level 3	231/2400 (9·6%)	231/2400 (9·6%)
Critical care unit level 2	1173/2400 (48·9%)	1193/2400 (49·7%)
Post-anaesthesia care unit	220/2400 (9·2%)	228/2400 (9·5%)
Surgical ward	776/2400 (32·3%)	748/2400 (31·2%)
Level of care on the first night after surgery		
Critical care unit level 3	225/2395 (9·4%)	238/2398 (9·9%)
Critical care unit level 2	1144/2395 (47·8%)	1204/2398 (50·2%)
Post-anaesthesia care unit	208/2395 (8·7%)	213/2398 (8·9%)
Surgical ward	818/2395 (34·2%)	743/2398 (31·0%)
Respiratory support after surgery (within 4 h of the end of surgery)		
Invasive mechanical ventilation	125/2397 (5·2%)	118/2397 (4·9%)
Non-invasive mechanical ventilation	19/2397 (0·8%)	190/2397 (7·9%)
High flow nasal oxygen therapy	49/2397 (2·0%)	42/2397 (1·8%)

Data are n (%) or n/N (%); denominators for summary measures vary due to missing data and patient withdrawal. A full summary of patient care characteristics and the number of patients with available data used for each summary measure are provided in the appendix (p 14). CPAP=continuous positive airway pressure. *Data were available for 2394 patients in the usual care group and 2392 patients in the CPAP group. †Data were available for 2393 patients in the usual care group and 2391 patients in the CPAP group.

Table 2: **Patient care**

197 (8·2%) of 2397 patients in the usual care group met the composite outcome (adjusted OR [aOR] 1·01 [95% CI 0·81–1·24]; p=0·95). No significant differences were identified in any of the secondary outcomes, including the individual components of the primary outcome, postoperative infection, or postoperative mechanical ventilation between the treatment groups (table 3, figure 2; appendix p 18). No significant differences were identified in the incidence of death 1 year after randomisation between the treatment groups (table 3). Details of other postoperative complications stratified by treatment group are in the appendix (pp 19–22). The median duration of the primary hospital admission was 8 days (IQR 6–13) in the usual care group and 9 days (6–13) in the CPAP group. 1451 (60·5%) of 2397 patients in the usual care group and 1526 (63·7%) of 2397 patients in the CPAP group were admitted to a critical care unit after surgery. The median duration of stay in critical care after surgery was 2 days (IQR 2–4) in the usual care group and 2 days (2–3) in the CPAP group. 242 (10·1%) of 2391 patients in the usual care group and 228 (9·5%) of 2395 patients in the CPAP group were re-admitted to hospital after initial hospital discharge within 30 days after randomisation (appendix p 23).

2241 patients received CPAP and thus were included in the safety population. 276 adverse events occurred in 200 (8·9%) of 2241 patients in the CPAP group (appendix pp 24–25). The most common adverse events associated with CPAP were claustrophobia (78 [3·5%] of 2241 patients), oronasal dryness (43 [1·9%]), intolerance due to excessive air leak (36 [1·6%]), vomiting (26 [1·2%]), and pain (24 [1·1%]). Seven (0·3%) of 2241 patients had breathing difficulty associated with CPAP. One patient had significant hearing loss, which lasted for 4 days after CPAP delivery using a hood device, and one patient's central venous catheter was obstructed by a CPAP hood, impeding a vasopressor infusion resulting in transient haemodynamic instability.

We did a planned per-protocol analysis using inverse probability weighting in accordance with the intervention that patients received (appendix pp 26–27). In a prespecified subgroup analysis, no significant differences were identified in the incidence of the composite primary outcome between the CPAP and usual care groups when stratified by surgical procedure category (appendix p 28). The incidence of the composite primary outcome was similar in patients who received CPAP compared with usual care (aOR 0·95 [95% CI 0·77–1·18]; p=0·66; appendix p 26). The proportion of patients who met the secondary outcomes were similar between the groups. In a post-hoc per-protocol analysis that included patients who were too unwell to receive CPAP or those who remained intubated after surgery and could not receive CPAP, the proportion of patients who met the primary and secondary outcomes remained similar between groups. In a post-hoc per-protocol analysis of patients who received CPAP for at least 4 h versus those who received usual care, the proportion of patients who met the primary and secondary outcomes remained similar between groups (appendix p 29). Investigator self-assessment of masking for determination of outcomes indicated a high rate of adherence to masking procedures (appendix p 18). In a post-hoc subgroup analysis of patients with an ARISCAT score greater than 45, no differences in the proportion of patients who met the primary outcome were identified between the CPAP and usual care group (OR 0·97 [95% CI 0·65–1·46]; p=0·91; appendix p 31).

A single unscheduled interim analysis was done at the request of the independent DMEC to establish whether there was any value in increasing the trial sample size in view of the lower than expected primary outcome event rate in the usual care group. Because we had decided to recruit no fewer than the prespecified sample of 4800 patients, we did not apply

	Usual care	CPAP	Adjusted OR (95% CI)	p value
Primary outcome*				
Pneumonia, endotracheal re-intubation, or death within 30 days of randomisation	197/2397 (8·2%)	195/2396 (8·1%)	1·01 (0·81–1·24)	0·95
Secondary outcomes†				
Pneumonia within 30 days of randomisation	117/2397 (4·9%)	123/2396 (5·1%)	1·06 (0·82–1·38)	0·66
Endotracheal re-intubation within 30 days of randomisation	90/2398 (3·8%)	80/2397 (3·3%)	0·89 (0·65–1·21)	0·45
All-cause mortality within 30 days of randomisation	33/2398 (1·4%)	30/2397 (1·3%)	0·91 (0·55–1·50)	0·71
Postoperative infection within 30 days of randomisation	741/2393 (31·0%)	738/2395 (30·8%)	0·99 (0·87–1·12)	0·89
Postoperative mechanical ventilation within 30 days of randomisation‡	210/2393 (8·8%)§	230/2395 (9·6%)¶	1·17 (0·94–1·45)	0·16
All-cause mortality within 1 year of randomisation	230/2363 (9·7%)	213/2374 (9·0%)	0·91 (0·75–1·11)	0·37

Data are n (%) or n/N (%); denominators for summary measures vary due to missing data and patient withdrawal. CPAP=continuous positive airway pressure. OR=odds ratio. The number of patients with available data and included in analysis for each summary measure is provided in the appendix (p 18). *Covariates used for the composite primary outcome were surgical procedure category, American Society of Anaesthesiology grade, age, smoking status, at least one comorbid disease, country, planned use of epidural, and sex (appendix p 119). †Covariates used for secondary outcomes were surgical procedure and planned use of epidural. ‡This outcome was recorded as receiving postoperative invasive or non-invasive mechanical ventilation within 30 days of randomisation, but did not include data from the process measure associated with ventilation in the 4 h period after the end of surgery. §168 patients received invasive mechanical ventilation, 21 patients received non-invasive mechanical ventilation, and 21 patients received both invasive and non-invasive mechanical ventilation. ¶166 patients received invasive mechanical ventilation, 38 patients received non-invasive mechanical ventilation, and 26 patients received both invasive and non-invasive mechanical ventilation.

***Table 3*: Primary and secondary outcomes**

any adjustment to the significance thresholds in the final analysis. The results of the interim analysis were reviewed solely by members of the DMEC, who recommended we continue recruitment without increasing the trial sample size.

In the prospective mixed methods process evaluation, we found wide variations in the experiences of patients who received CPAP and the clinical staff who delivered the intervention. The main influences on this variability were the characteristics of the intervention itself and the local context (eg, hospital culture, systems, and resources). We found that a substantial proportion of patients did not like or were unable to tolerate CPAP. Claustrophobia, nausea, pain, feeling too hot, excessive dryness of the mouth or eyes, and inability to communicate with relatives were the most common barriers to CPAP delivery. Patient accounts ranged from vague recollections of receiving CPAP to vivid descriptions of how unpleasant they found it. Of the patients who could recall receiving the intervention clearly, none completed 4 h of treatment. Hospitals that were more successful in delivering the intervention were more likely to have integrated CPAP into postoperative care at the perceived optimal time, early after surgery when patients often remained drowsy. Additionally, staff at the more successful hospitals seemed highly invested in delivering the intervention and helping patients to tolerate CPAP.

Discussion

The principal finding of the PRISM trial was that preventative CPAP started early after major open abdominal surgery, lasting for at least 4 h, did not reduce the incidence of postoperative pneumonia, endotracheal re-intubation, or death at 30 days. This effect did not differ in any of the prespecified subgroups or the

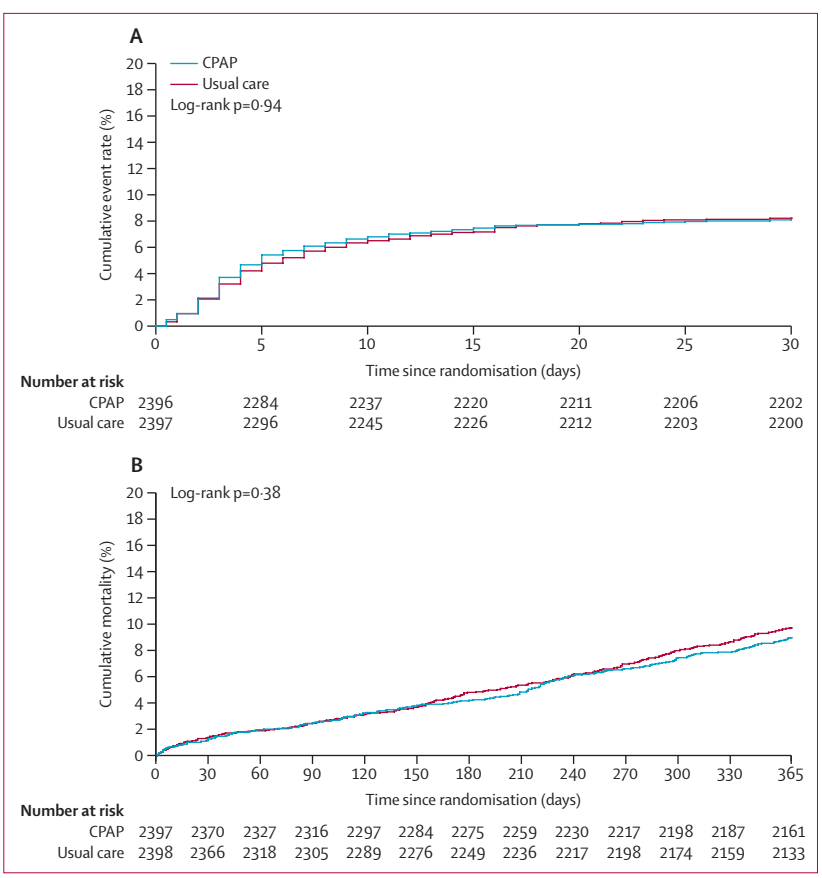

***Figure 2*: Time to composite primary outcome 30 days after randomisation in the ITT population (A) and time to all-cause mortality 1 year after randomisation in 4795 patients (B)**
Denominators for the time to event analysis and secondary outcome of all-cause mortality 1 year after randomisation differ because all patients who were followed-up for up to 30 days, but were censored after this timepoint have been included in the plot. CPAP=continuous positive airway pressure.

per-protocol analysis done according to the intervention patients received. These results do not support the widespread adoption of postoperative CPAP as a preventative measure to prevent postoperative respiratory complications. When comparing these findings with those of smaller efficacy trials,[15] it seems likely that various barriers to the successful routine delivery of CPAP to all patients after major abdominal surgery decrease the real-world clinical effectiveness of this approach.

Previous research, mostly from small trials done at single centres, suggests that preventative CPAP early after major surgery might prevent subsequent respiratory complications, perhaps by reducing atelectasis and pulmonary collapse.[15–17] This previous evidence also suggest that CPAP might improve outcomes among patients who develop respiratory failure after major surgery.[16,17] The findings of a Cochrane review, which identified ten trials including around 700 patients, suggest that preventative CPAP might prevent pneumonia, re-intubation, and invasive ventilation after major surgery. However, the authors of the systematic review concluded that further high quality research was needed to confirm this finding.[15] One of the largest trials to date by Squadrone and colleagues, evaluated the efficacy of CPAP in preventing re-intubation among 209 patients who developed respiratory failure after major abdominal surgery across 15 hospitals.[16] The investigators found that patients receiving CPAP had a lower incidence of pneumonia and re-intubation than did patients given standard care. In a multicentre trial of non-invasive ventilation in 293 patients who had undergone abdominal surgery, Jaber and colleagues reported an increase in ventilator-free days compared with standard oxygen therapy and a reduction in health-care associated infections.[29] The results of these studies contrast with our findings, perhaps because they relate to the focused use of respiratory support amongst patients who are already hypoxaemic. In the PRISM trial, we assessed CPAP as a preventative measure to prevent respiratory failure, and so recruited a much wider patient population than previous trials in which this approach has been used as a therapeutic measure to treat postoperative hypoxaemia.[16] These two phase two trials, where the intervention was tightly controlled, are not readily comparable to PRISM, which is a pragmatic clinical effectiveness trial investigating the real-world implementation of CPAP in post-anaesthesia care units.

The trial protocol allowed for CPAP to be commenced within 4 h of the end of surgery because some centres had to transfer patients to a critical care unit to deliver CPAP as a local standard of care, reflecting the reality of intervention delivery. The median interval between the end of surgery and the start of CPAP was 90 min. In a 2018 study, the iPROVE investigators assessed the effectiveness of three intraoperative ventilation strategies in combination with postoperative CPAP to prevent postoperative complications in 967 patients, of whom 723 received CPAP. Similar to the results of our trial, CPAP was not associated with any reduction in the incidence of postoperative complications compared with standard care.[30]

CPAP is a familiar and commonly used treatment for acute respiratory failure, but little data is available regarding safety of the intervention.[31–33] The results of the PRISM trial suggest that CPAP is a safe treatment, with only two serious adverse events observed in the 2241 patients who had the intervention. Our data suggest that one in ten patients will have minor problems with CPAP delivery that might require adjustment or discontinuation of the treatment. We observed that patients in the CPAP group often received non-invasive mechanical ventilation during the intervention period. However, few adverse events were reported that indicated respiratory failure among CPAP group patients during the intervention period. The likely explanation for this observation is that clinicians chose to administer non-invasive ventilation in preference to CPAP considering the ease of switching between CPAP and non-invasive ventilation on many delivery devices.

Our trial had several strengths. We included a large sample of patients, representative of a broad spectrum of contemporary surgical and perioperative practice making the results widely generalisable. We used clearly defined outcome definitions and collected data using a standardised case report form. The statistical analysis was done according to intention-to-treat principles using a pre-specified analysis plan. The pragmatic nature of the trial takes into account barriers to intervention delivery encountered in routine clinical practice, which we assessed through an embedded mixed methods process evaluation. Most patients had lower gastrointestinal, hepatobiliary, or other intra-peritoneal surgery, whereas a smaller proportion of patients had upper gastrointestinal surgery. This difference is likely due to concerns about the effects of positive pressure on anastomotic healing following this type of surgery, although none of the available evidence suggests that CPAP is harmful in this situation.[34] In the PRISM trial, the incidence of anastomotic leak was similar in all patient subgroups. Our trial also had some limitations. We allowed clinicians to choose from three CPAP interface devices, the facemask, hood, and nasal mask, to represent the range of CPAP devices currently available for clinical use. Clinicians selected an interface device after discussion with individual patients, although not every device was available in every hospital. Although training was offered for all interface devices, the choice of device might have been influenced by staff familiarity with certain types of equipment. Consequently, there was an unequal distribution of CPAP interface devices. The delivery devices also differed between hospitals, according to local policy and equipment availability. At the beginning of the trial, local investigators were permitted to randomly assign patients at any point before the end of surgery.

However, in some cases patients in the intervention group did not receive CPAP because they were either too unwell to receive CPAP in the immediate postoperative period or in some cases remained intubated immediately after the end of surgery. Therefore, we amended the protocol after the trial started to ensure investigators randomly assigned patients at the end of surgery. PRISM was a pragmatic trial that assessed the clinical effectiveness of CPAP in a real-world context. We did not therefore expect 100% compliance with the trial intervention, and we made allowance for this in our sample size calculation, anticipating a smaller treatment effect than anticipated under optimum circumstances. 93·5% of patients allocated to the intervention received CPAP. Examples of situations when patients did not receive the intervention include remaining intubated after surgery and patient refusal. Two-thirds of patients who received CPAP received the treatment for 4 h. These findings are likely to represent the proportion of patients who would receive the full course of CPAP in routine practice. However, the observation that a third of patients were unable to tolerate 4 h of CPAP is an important finding that might affect the future use of CPAP in this setting. To test the impact of intervention compliance on clinical effectiveness, we did a post-hoc per-protocol analysis including only patients who received CPAP for 4 h. The treatment effect in this analysis was similar to our primary analysis that included all patients, indicating that the absence of clinical effectiveness was not due to poor intervention compliance. This interpretation is further supported by the findings of our process evaluation, which showed that the delivery of the trial intervention within the complex system of postoperative care was difficult in many hospitals. The ability to deliver CPAP early after surgery, when patients remained drowsy, with careful attention to patient tolerance and comfort, seemed to improve trial intervention compliance. It was not feasible to mask patients and clinicians involved in the delivery of CPAP to group allocation due to the nature of the intervention. However, we controlled this bias through blinded outcome assessment and we achieved good compliance with these procedures. The proportion of patients who met the composite primary outcome (8·2%) was lower than the estimate we used in our sample size calculation (11·7%). The trial was well powered with strong external generalisability, and it is highly unlikely that a larger sample size would alter our findings. Additionally, although the observed incidence of complications was lower than expected, the preoperative ARISCAT score, which predicts postoperative respiratory morbidity, classified the trial population as being at intermediate-to-high risk of respiratory complications. Thus, it is possible that a trial of very high risk patients (ARISCAT score >45) might provide different results.

In patients aged 50 years and older undergoing major open abdominal surgery, the application of CPAP within 4 h of the end of surgery did not result in lower incidence of pneumonia, re-intubation, or death at 30 days. These results do not support the widespread adoption of routine postoperative CPAP as a preventative measure to prevent early postoperative respiratory complications.

Contributors

RMP, VMR, and AR conceptualised the study. RMP, TEFA, AR, BCK, and VMR designed the study. All authors were involved in data acquisition. AP, BCK, TEFA, RMP, and VMR analysed and interpreted the data. AP and BCK accessed and verified the data. TEFA and RMP drafted the manuscript. The PRISM writing committee critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication. The corresponding author had full access to trial data and takes final responsibility for the decision to submit for publication.

Declaration of interests

RMP reports grants from National Institute for Health Research, grants and non-financial support from Intersurgical UK, during the conduct of the study; grants and personal fees from Edwards Life Sciences, outside of the submitted work; has given lectures or done consultancy work for Nestle Health Sciences, BBraun, Intersurgical, GlaxoSmithKline, and Edwards Lifesciences; and is on the editorial board for the *British Journal of Anaesthesia* and the *British Journal of Surgery*. TEFA reports grants from Medical Research Council, during the conduct of the study; has done consultancy work for Merck Sharp & Dohme, outside of the submitted work; and is a member of the associate editorial board of the *British Journal of Anaesthesia*. CA is a member of the associate editorial board of the *Revista Española de Anestesiologia y Reanimación* and *Frontiers*. TS is an associate editorial board member for *Trials*, *Frontiers in Microbiology*, *Medicine*, and *Critical Care Explorations*. MC reports consultancy and speaker fees from B Braun and Edwards Lifesciences; and is deputy editor-in-chief for the *European Journal of Anaethesiology*. All other members of the writing committee declare no competing interests.

Data sharing

The trial steering committee will consider requests for access to deidentified trial data by researchers, according to a prespecified statistical analysis plan and with a data sharing agreement. Data will be available at the time of publication. Data access requests should be made to admin@prismtrial.org. The full set of trial documents, including the trial protocol, statistical analysis plan, and informed consent forms are available on the trial website (prismtrial.org).

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