Hypercapnia versus normocapnia for emergence from desflurane anaesthesia

Single-blinded randomised controlled study

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Background

- After cessation of general anaesthetics, depth of anesthesia progressively reduces and the patients enter a relatively light anesthesia level in which external stimuli, such as body touch or tracheal tube presence, may cause unexpected large body movements

- Respiratory complications occur more frequently during emergence from anesthesia compared with anesthesia induction and fatal outcomes have been documented.

Background

- Emergence from inhalational general anesthesia is facilitated by elimination of the inhalational anesthetic through pulmonary ventilation.

- However, increased mechanical ventilation during the emergence process usually results in hypocapnia which delays spontaneous breathing recovery due to decreased ventilatory drive and possibly leads to reduced cardiac output and cerebral blood flow.

Background

- Previous studies produced hypercapnia hyperventilation, which was deliberately produced by carbon dioxide infusion into the inspired gas mixture or by rebreathing combined with anesthetic gas absorption. These interventions achieved faster emergence.

- Hypercapnia increases the ventilatory drive even under general anesthesia and stabilizes breathing during sleep. Furthermore, it has been observed to depress the laryngeal reflexes and improve cardiovascular stability in humans under enflurane anesthesia.

Background

- Hypothesize

"Hypercapnia produced by hypoventilation before initiation of emergence shortens emergence time from general anesthesia"

Methods

- Trial Design
  - Prospective, single-blinded, randomized controlled trial
  - Approved by Ethical Committee of Chiba University Hospital, Chiba, Japan.
  - Informed consent from all participants.

Methods

- Patients : Adult patients undergoing abdominal surgery under desflurane anesthesia.

- Invention : “Hypercapnia group” Maintained ET-CO_2 approximate 60 mmHg at emergence from anesthesia.

- Control : “Normocapnia group” Maintained ET-CO_2 between 30 and 35 mmHg at emergence from anesthesia.

Methods

- Primary outcome
  - Emergence time from general anesthesia
- Secondary outcomes
  - Undesirable cardiorespiratory events

Methods

- Undesirable cardiorespiratory events
  - Tachycardia : Heart rate more than 120 beats/min for more than a minute
  - Bradycardia : Heart rate less than 50 beats/min for more than a minute
  - Hypertension : SBP greater than 160 mmHg for more than a minute
  - Hypotension : SBP less than 80 mmHg for more than a minute

Methods

- Undesirable cardiorespiratory events
  - Hypopnea : Reduction of either airflow or capnogram wave more than 50% for more than 10 sec
  - Apnea : Cessation of either airflow or capnogram wave for more than 10 sec
  - Bradypnea : Respiratory rate less than 10 breath/min
  - Tachypnoea : Respiratory rate faster than 30 breath/min

Methods

- Undesirable cardiorespiratory events
  - Irregular breathing : More than 50% changes of respiratory wave or frequency within 10 sec
  - Cough reflex : Rapid expiratory flow wave(s) more than double of quiet breathing or capnogram wave with cough behavior on video-images
  - Desaturation : SpO2 reduction more than 2%.

Methods

- Inclusion criteria
  - Adult patients (20 to 70 years old)
  - Scheduled abdominal surgery under general anesthesia combined with
    - Epidural anesthesia
    - Intra-operative arterial blood pressure monitoring.

Methods

- Exclusion criteria
  - American Society of Anesthesiologists physical status (ASA-PS) greater than 3
  - Abnormal airway
  - Post-head and neck surgery
  - Tracheostomy

Methods

- Exclusion criteria
  - Asthma
  - COPD (%FEV1.0< 70%)
  - Obesity hypoventilation syndrome
  - Intracranial diseases
  - Scheduled extubation at ICU.

Methods

- Criteria for stopping the study
  - Difficult tracheal intubation
  - Intraoperative severe cardiorespiratory complications
  - Intraoperative hypoxemia with P/F ratio < 200
  - Emerged risks for tracheal extubation in the operating room

Methods : Sample size

- No previous study has assessed effect of hypercapnia on emergence time for desflurane anesthesia.

- Emergence time in desflurane anesthesia was reported to be 6±2min [mean± SD] and hypercapnia was reported to shorten emergence from sevoflurane anesthesia by 2.4 min (28%).

- In order to detect the 1.7 min difference between the groups with a = 0.05 (two-tailed) and b = 0.8, the suitable sample size was calculated to be 23 individuals for each group. Accordingly, the total sample size was set as 50 patients.

Methods : Randomization

- Participants were randomly assigned to either normocapnia group or hypercapnia group at a 1 : 1 ratio

- By employing the minimization method with biased coin assignment balancing for sex and age (>64 or <64 years)

- The randomization result was communicated to the anesthesiologist, but not to the participant.

Study protocol : Anesthesia management

- After epidural catheter placement, general anesthesia was induced by
  - Intravenous injection of fentanyl (2mg/kg)
  - Remifentanil (0.1 to 0.5 mg/kg IBW/min)
  - Propofol 1 to 2 mg/kg

- A polyvinyl chloride cuffed tracheal tube (6.5 to 7.5 mm I.D.) was inserted into the trachea after complete neuromuscular blockade with rocuronium 1 mg/kg.

Study protocol : Anesthesia management

- General anesthesia was maintained with desflurane inhalation 3 to 5% and remifentanil infusion combined with epidural anesthesia (either levobupivacaine or ropivacaine).

- Depth of neuromuscular block was monitored by an acceleromyograph neuromuscular monitoring (TOF watch) and maintained by additional 10 to 20 mg rocuronium injection(s).

Study protocol : Anesthesia management

- Anesthesia depth was monitored and maintained with BIS 40 to 60 (BIS)

- Normocapnia was maintained by adjusting the ventilator settings (8 ml/IBW tidal volume, 5 to 10 cmH_2O PEEP).

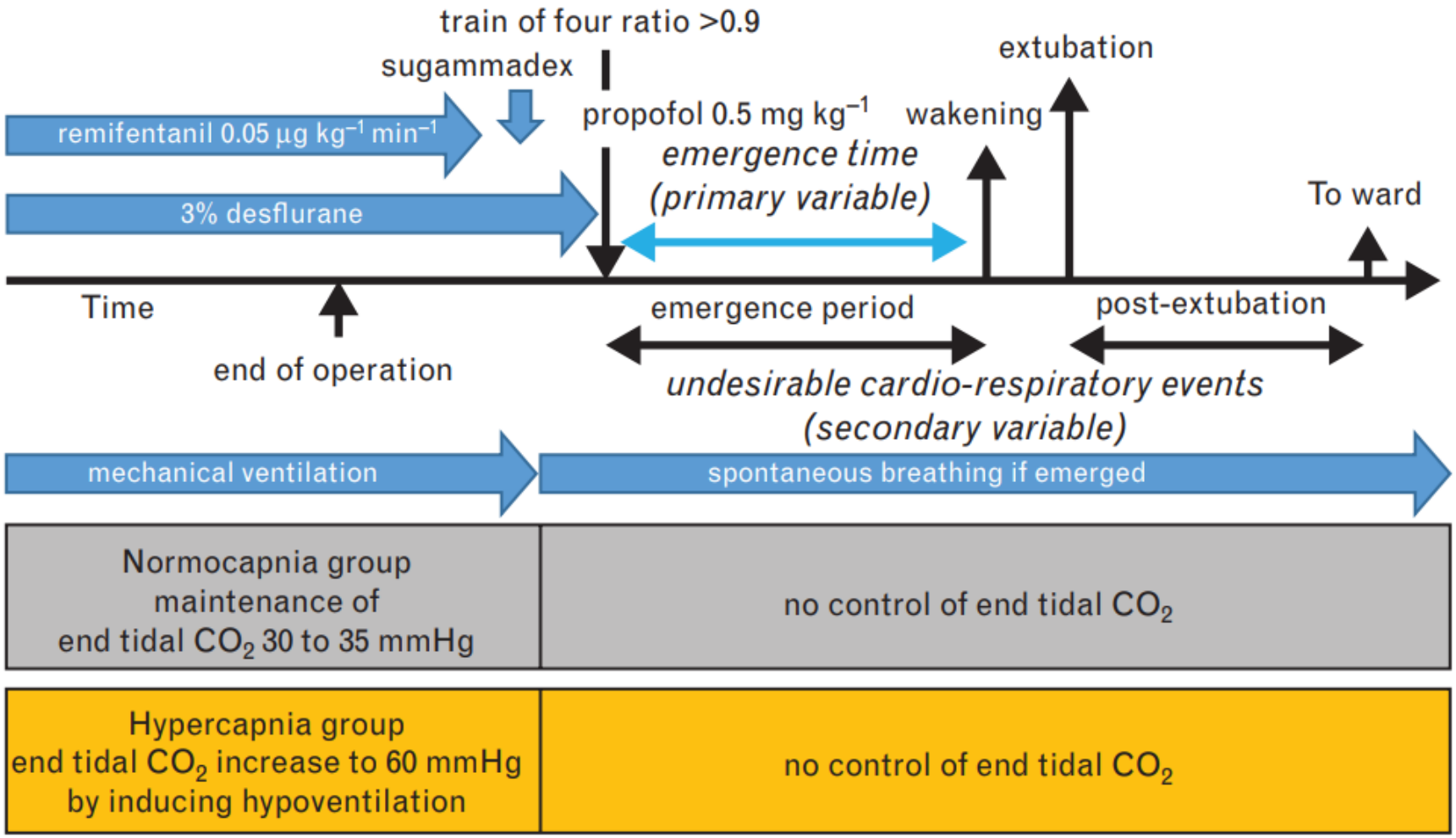
- Core temperature was maintained above 36^{o}C, and hemodynamics were normalized by fluid infusion, blood transfusion and vasopressor during surgery.

Study protocol : Anesthesia management

- Flurbiprofen 1 mg/kg was intravenously administered at 30 to 60 min before predicted end of surgery.

- Epidural continuous infusion drug was started with the mixture of 0.125% levobupivacaine 200 ml, fentanyl 800 mg, droperidol 2.5 mg at a rate of 4 ml/hr at the end of surgery.

Study protocol : Emergence from anesthesia



Study protocol : Emergence from anesthesia

- End-tidal desflurane concentration was maintained at 3% for at least 10 min before termination of desflurane inhalation.

- When coughs occurred from placing the X-ray board into the back immediately after surgery, 0.5 mg/kg propofol was administered to stabilize ventilation.

Study protocol : Emergence from anesthesia

- Approximately 5 min before desflurane cessation, remifentanil infusion was terminated and appropriate dose of sugammadex was administered based on depth of neuromuscular blockade determined by the acceleromyograph neuromuscular monitoring (2 mg/kg for train-of-four count of 2 or higher, and more than 4 mg/kg for post-tetanic count of 2 or higher).

- Inhaled oxygen concentration was increased to 86% (5 LPM oxygen and 1 LPM air). After confirmation of train-of-four ratio 0.9, desflurane was terminated, and propofol 0.5 mg/kg was intravenously injected to reduce incidence of emergence agitation as this is a common practice in our institute.

Study protocol : Emergence from anesthesia

- ET-CO_2 was maintained between 30 and 35 mmHg in normocapnia group with pressure-controlled ventilation

- In hypercapnia group, tidal volume and respiratory rate were adjusted to approximate the ET-CO_2 60 mmHg.

- When spontaneous breaths emerged before emergence from anesthesia, the mechanical ventilation was ceased. No control of the ET-CO_2 was attempted during spontaneous breathing, which allowed a normalization of ET-CO_2

Study protocol : Emergence from anesthesia

- When return of consciousness was confirmed by the predefined criteria below, the patient was instructed to take a deep breath, after which the tracheal tube was removed.

- In order to avoid external stimuli to breathing and consciousness after extubation, the anesthesiologist refrained from external stimulation: calling the patient's name, verbally urging breathing or touching the patient for at least for 10 min after extubation

Study protocol : Primary outcome

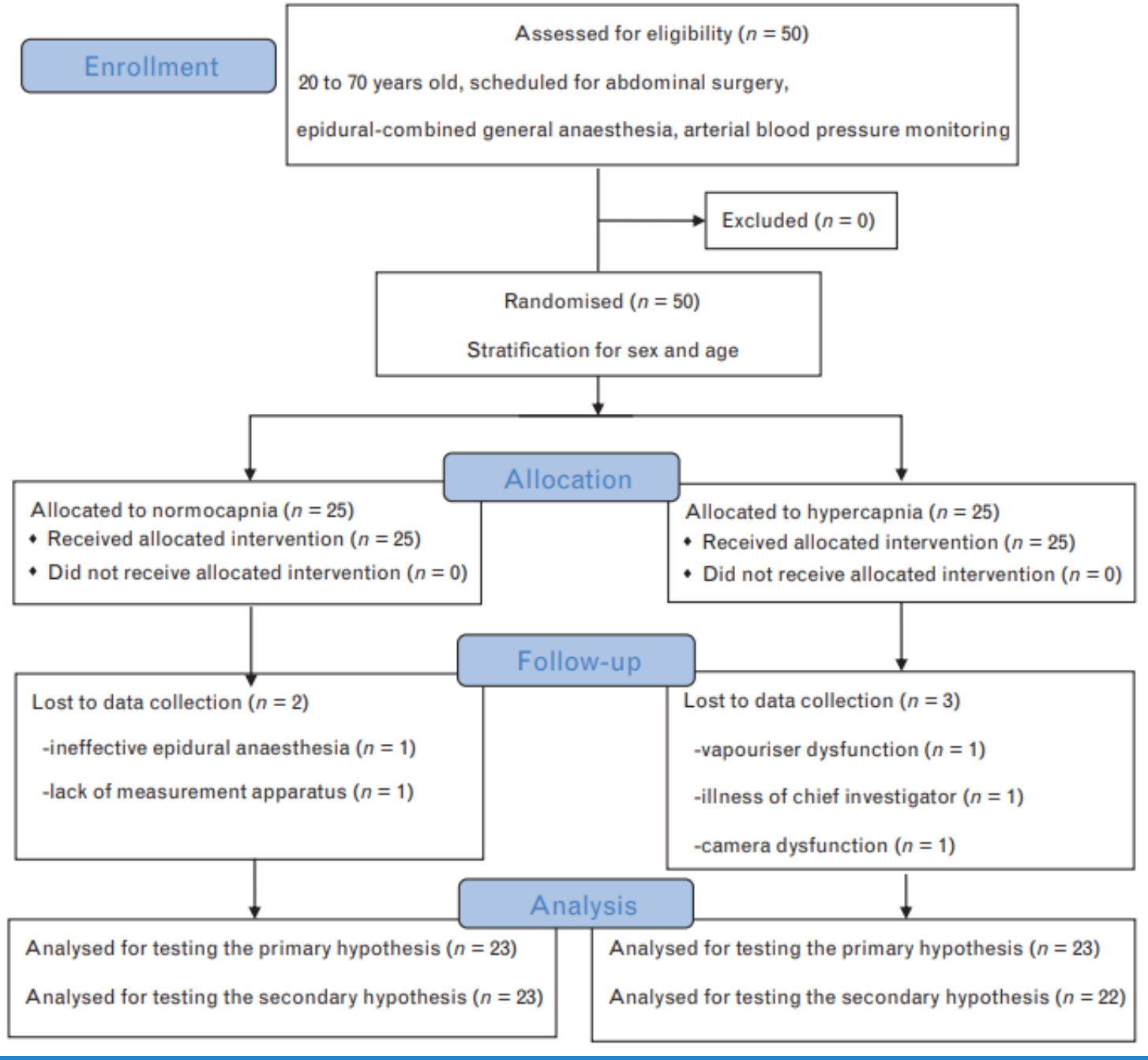
- The primary outcome for the trial was emergence time from general anesthesia defined as the time between desflurane cessation and emergence of consciousness confirmed by spontaneous eye opening and response to a verbal command (mouth opening).

- During emergence from anesthesia for the initial 15 min, there were no stimuli to the patient such as whispering, verbal commands and touching until there was spontaneous eye opening.

- When the patient's spontaneous arousal was not observed during the initial 15 min, the name of the patient was called out by the anesthesiologist along with soft shoulder touching.

Statistical analysis

- Continuous variables : Mean values and SD
- Categorical data : frequencies and proportions
- Primary outcome : Independent two-sample t-test.
- Secondary outcomes : Fisher exact tests
- Statistical analysis was performed by SAS software version 9.4 and SigmaPlot 12.0


Enrollment
Assessed for eligibility (n = 50)
20 to 70 years old, scheduled for abdominal surgery,
epidural-combined general anaesthesia, arterial blood pressure monitoring
Excluded (n = 0)
Randomised (n = 50)
Stratification for sex and age
Allocation
Allocated to normocapnia (n = 25)
• Received allocated intervention (n = 25)
• Did not receive allocated intervention (n = 0)
Allocated to hypercapnia (n = 25)
• Received allocated intervention (n = 25)
• Did not receive allocated intervention (n = 0)
Follow-up
Lost to data collection (n = 2)
-ineffective epidural anaesthesia (n = 1)
-lack of measurement apparatus (n = 1)
Lost to data collection (n = 3)
-vapouriser dysfunction (n = 1)
-illness of chief investigator (n = 1)
-camera dysfunction (n = 1)
Analysis
Analysed for testing the primary hypothesis (n = 23)
Analysed for testing the secondary hypothesis (n = 23)
Analysed for testing the primary hypothesis (n = 23)
Analysed for testing the secondary hypothesis (n = 22)

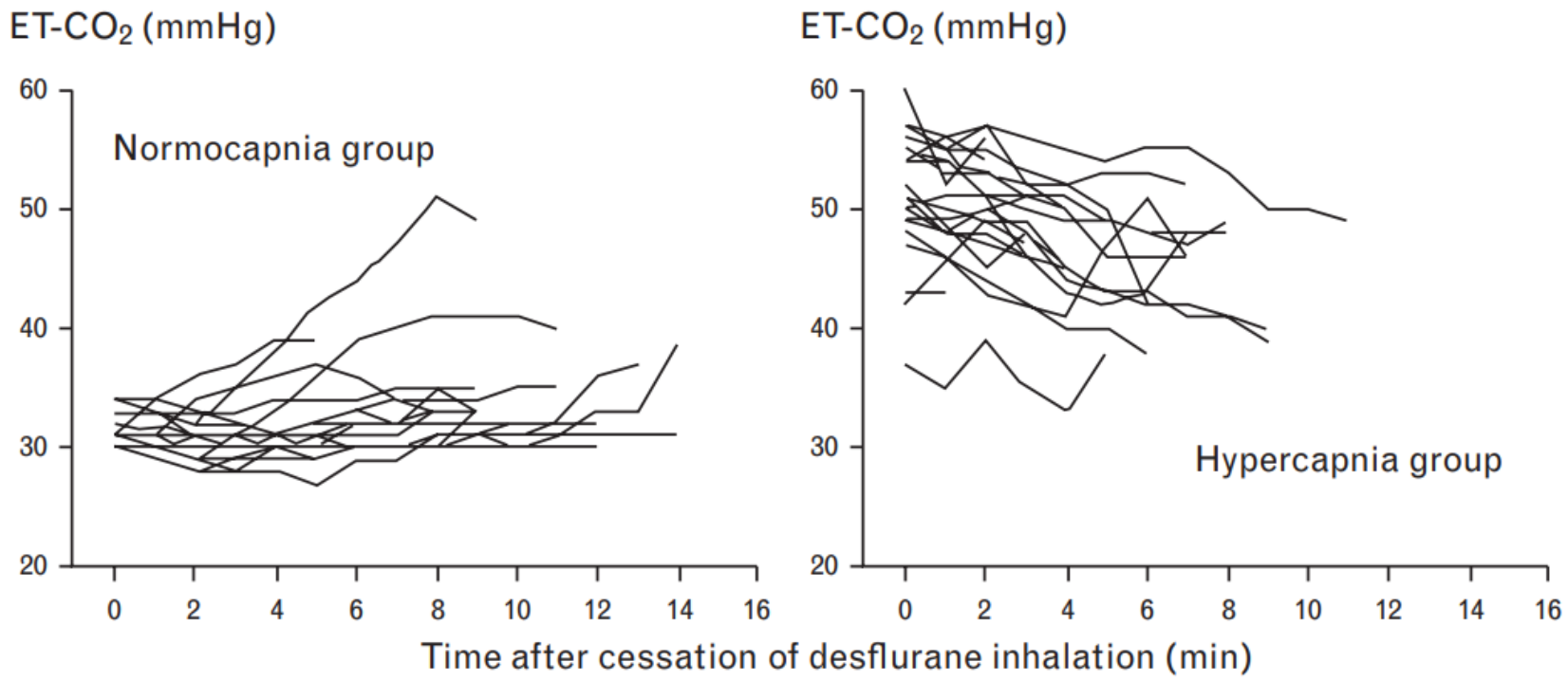
Res

Table 1 Background characteristics of participants, surgery and anaesthesia

	Normocapnia group	Hypercapnia group
Patient characteristics		
Number of individuals	23	23
Male	8 (35%)	8 (35%)
Age (years)	52.3 ± 12.5	52.2 ± 13.2
Height (cm)	160 ± 8.2	163 ± 9.6
Weight (kg)	62.9 ± 16.4	63.9 ± 15.6
BMI (kg m_{-2})	24.3 ± 5.5	24.0 ± 4.5
Neck circumference (cm)	36.0 ± 4.6	35.6 ± 4.0
Waist circumference (cm)	85.7 ± 11.8	86.2 ± 12.3
Waist-hip ratio	0.865 ± 0.072	0.860 ± 0.087
Pre-operative airway assessments		
Mallampati Class (I / II / III / IV)	(13 / 3 / 7 / 0)	(11 / 5 / 6 / 1)
Thyromental distance (mm)	85 ± 15	87 ± 13
Mouth opening (mm)	48 ± 6	46 ± 8
Upper lip bite test (I / II / III)	(16 / 7 / 0)	(18 / 4 / 1)
Pre-operative sleep study		
Apnoea Hypopnoea Index (AHI) (h^{-1})	8.8 ± 10.0	6.6 ± 8.8
number of patients with AHI $> 5\,h^{-1}$	11 ± 50	8 ± 36
Mean nadir SpO_2 (%)	93.5 ± 1.8	94.2 ± 2.1
Pre-operative cardiopulmonary comorbidities		
ASA-PS (1 / 2 / 3)	(9 / 14 / 0)	(12 / 11 / 0)
Smoking history (no / current / past)	(10 / 1 / 12)	(13 / 0 / 10)
Hypertension / ischemic heart disease / COPD	(4 / 0 /0)	(5 / 0 / 0)
Surgical characteristics		
Operation time (min)	237 ± 122	248 ± 111
Laparotomy / laparoscopy	22 (96%) / 1 (4%)	21 (91%) / 2 (9%)
Lower abdominal surgery	16 (70%)	16 (70%)
Gynaecological surgery	15 (65%)	13 (57%)
Colon or rectal surgery	1 (4%)	3 (13%)
Upper abdominal surgery	7 (30%)	7 (30%)
Hepatobiliary surgery	5 (22%)	3 (13%)
Upper gastrointestinal tracts surgery	1 (4%)	3 (13%)
Other upper abdominal surgery	1 (4%)	1 (4%)
Anaesthesia drugs		
Propofol ($mg\,kg^{-1}$)	1.9 ± 0.5	1.8 ± 0.4
Remifentanil ($mg\,kg^{-1}$)	0.03 ± 0.02	0.03 ± 0.02
Fentanyl ($\mu g\,kg^{-1}$)	2.8 ± 1.5	3.9 ± 1.3
Rocuronium ($mg\,kg^{-1}$)	1.9 ± 0.7	2.0 ± 0.8
Sugammadex ($mg\,kg^{-1}$)	2.1 ± 0.1	2.1 ± 0.1

Values are number (proportion) and mean ± SD. Data are missing in one patient in hypercapnic group and one patient in normocapnic group.

Fig. 3 Change of end-tidal carbon dioxide concentration (ET-CO_2) after cessation of desflurane inhalation



Each connected line represents individual ET-CO_2 changes for normocapnic (left: $n = 23$) and hypercapnic (right: $n = 21$) groups. Note constant ET-CO_2 level in normocapnic group except three patients who recovered spontaneous breathing and increased ET-CO_2. In contrast, higher ET-CO_2 at desflurane cessation progressively decreased during emergence period in hypercapnic group.

Results

- Emergence from desflurane anesthesia (primary outcome variable) was significantly faster in the hypercapnia group than the normocapnia group [normocapnia: 9.4 ± 2.4 min, hypercapnia: 5.5 ± 2.6 min, $P < 0.001$] supporting the primary hypothesis of this study.

- Hypercapnia shortened the emergence time by 3.8 min (40%) on average [95% CI: 2.4 to 5.3]

Results

- Multiple linear regression analysis was performed by using
  - Six background variables (group, sex, age, BMI, smoking history and pre-operative apnea hypopnea index),
  - Six dynamic variables at desflurane cessation (bispectoral index, end tidal desflurane concentration, remifentanil effect site concentration, fentanyl effect site concentration, minute volume and estimated cardiac output) and operation period.

Results

Table 3 **Results of multiple linear regression analysis: independent predictors for the emergence time**

Variable	Estimate	Standard error	Standardised partial regression coefficients	*P*
Intercept	1.16	2.84	0	0.68
Group (normocapnia = 1, hypercapnia = 2)	−2.98	0.712	−0.49	<0.001
Age	0.0501	0.0257	0.21	0.056
BMI	0.216	0.072	0.35	0.005
Fentanyl effect site concentration at cessation of desflurane	4.04	1.63	0.29	0.018
Estimated cardiac output[a] at cessation of desflurane	−0.249	0.126	−0.24	0.056

[a] Cardiac output was estimated by 0.002(heart rate)∗(pulse pressure) based on the study by Hill *et al.*[26]

Fig. 4 Results of secondary outcome: Group comparisons of incidence of undesirable cardiorespiratory events during emergence period (left) and postextubation period (right)

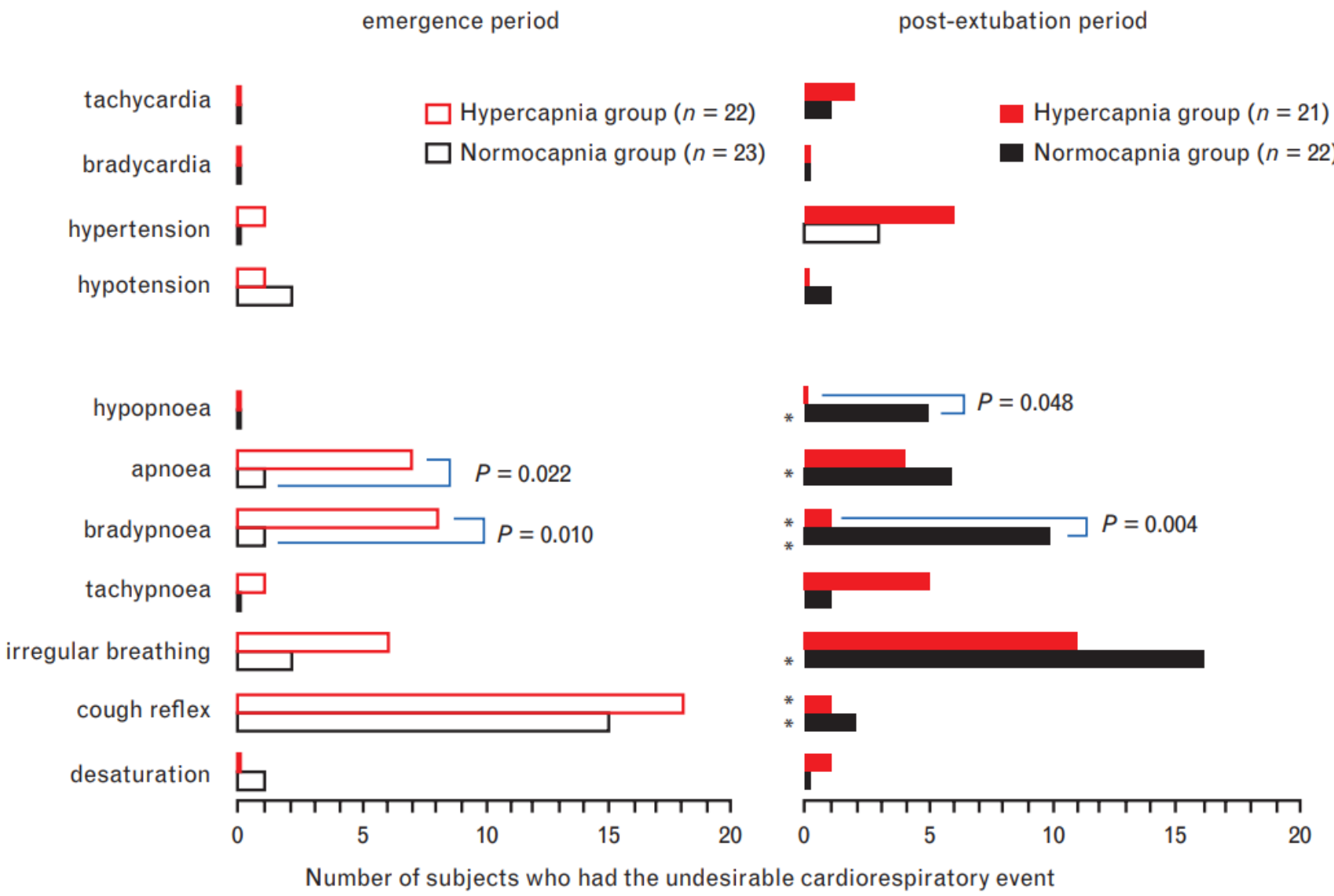
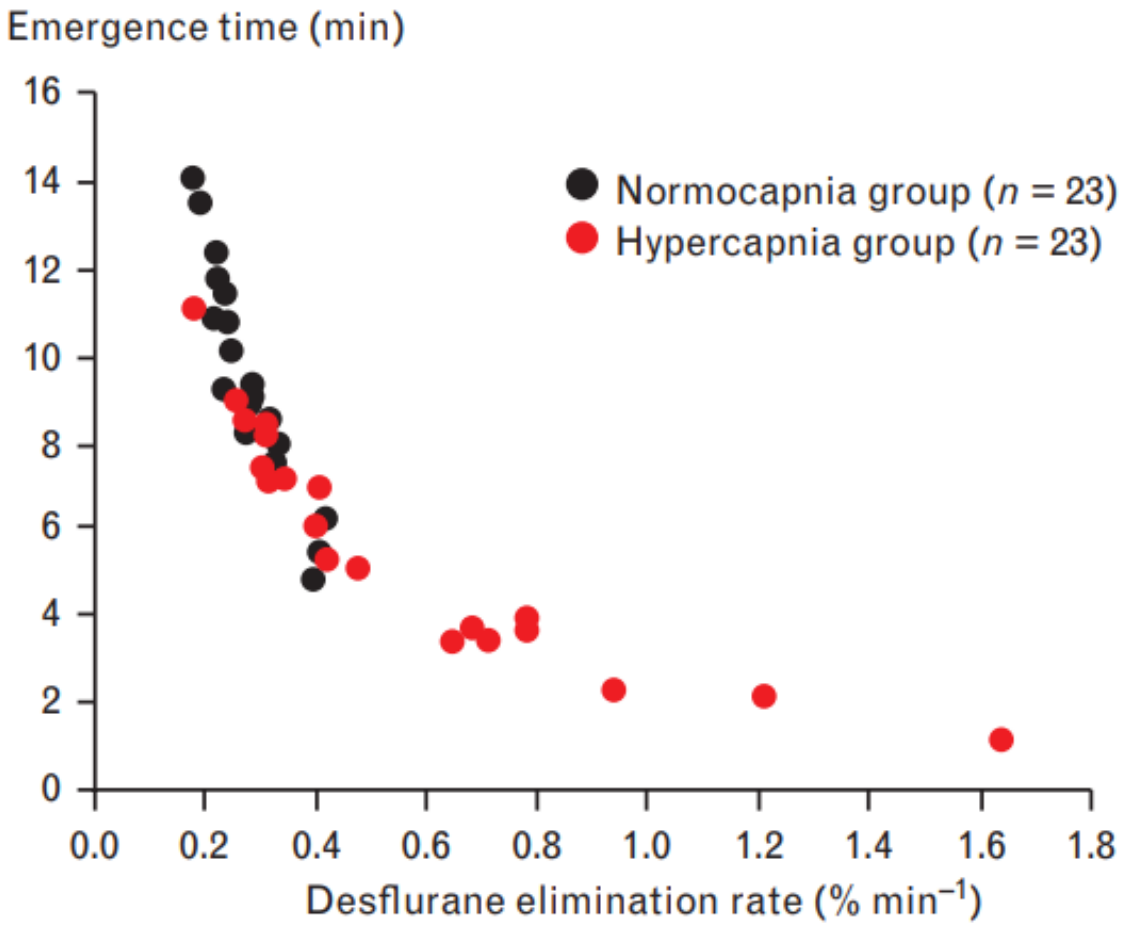


Table 2 Changes of anaesthesia depth, respiratory and cardiovascular status during emergence from general anaesthesia

Groups (normocapnia: $n = 23$, hypercapnia: $n = 23$)	At desflurane cessation			At emergence from anaesthesia		
	Normocapnia	Hypercapnia	*P*	Normocapnia	Hypercapnia	*P*
Anaesthesia depth						
End-tidal desflurane concentration (%)	3.1 ± 0.2	3.0 ± 0.2	0.236	0.6 ± 0.2	0.6 ± 0.3	0.699
Propofol effect site concentration ($\mu g\,ml^{-1}$)	0.11 ± 0.24	0.12 ± 0.26	0.868	0.55 ± 0.22	0.60 ± 0.32	0.511
Remifentanil effect site concentration ($\mu g\,ml^{-1}$)	0.54 ± 0.22	0.50 ± 0.17	0.497	0.18 ± 0.07	0.24 ± 0.09	0.013
Fentanyl effect site concentration ($\mu g\,ml^{-1}$)	0.49 ± 0.25	0.48 ± 0.20	0.960	0.19 ± 0.06	0.27 ± 0.09	0.002
Bispectral Index	64 ± 12	68 ± 14	0.325	75 ± 16	76 ± 18	0.811
Respiratory variables						
Endtidal carbon dioxide concentration (%)	31 ± 1	52 ± 6	<0.001	35 ± 6	49 ± 6[a]	<0.001
Patients who recovered spontaneous breathing	0 (0%)	19 (83%)	<0.001	3 (13%)	22 (96%)	<0.001
Respiratory rate ($rate\,min^{-1}$)	13.2 ± 1.8	9.0 ± 3.7	<0.001	12.9 ± 1.8	12.5 ± 3.3[a]	0.603
Tidal volume ($ml\,min^{-1}$)	515 ± 78	576 ± 268	0.307	478 ± 99	486 ± 152[a]	0.817
Minute ventilation ($l\,min^{-1}$)	7.0 ± 1.5	4.3 ± 1.8	<0.001	5.3 ± 1.3	5.70 ± 1.6[a]	0.586
Cardiovascular variables						
SBP (mmHg)	100 ± 15	104 ± 18	0.484	110 ± 17	115 ± 22[a]	0.390
DBP (mmHg)	48 ± 8	46 ± 10	0.472	53 ± 10	53 ± 12[a]	0.992
Mean arterial pressure (mmHg)	66 ± 10	66 ± 12	0.974	72 ± 12	74 ± 15[a]	0.665
Pulse pressure (mmHg)	52 ± 9	57 ± 12	0.087	58 ± 10	63 ± 14[a]	0.168
Heart rate ($rate\,min^{-1}$)	65 ± 10	80 ± 15	<0.001	68 ± 12	83 ± 15[a]	<0.001
Estimated cardiac output[b] ($l\,min^{-1}$)	6.7 ± 1.7	9.3 ± 3.3	0.002	7.8 ± 1.6	10.6 ± 3.7[a]	0.002

Values are number (proportion) and mean ± SD. [a] $n = 22$. [b] Cardiac output was estimated by 0.002 (heart rate)∗(pulse pressure) based on the study by Hill *et al.*[26]

Fig. 5 An inversed curvilinear relationship between the emergence time from desflurane anaesthesia and desflurane elimination rate



Discussion

- It was evident that emergence from desflurane anesthesia was faster in patients with hypercapnia supporting the primary hypothesis, hypercapnia facilitated recovery of spontaneous breathing before cessation of desflurane inhalation and decreased incidences of hypopnea and bradypnea immediately after tracheal extubation supporting the secondary hypothesis.

- Posthoc linear regression analysis identified five independent predictors including hypercapnia, age, BMI, fentanyl effect site concentration and estimated cardiac output at cessation of desflurane for rapid emergence from desflurane anesthesia.

Discussion

- Carbon dioxide is a physiological respiratory stimulant and mild hypercapnia was demonstrated to decrease abnormal breathings, such as central and obstructive apneas in sleeping humans.

- Respiratory stabilizing effects of hypercapnia after tracheal extubation found in anaesthetized individuals in this study agree with the previous findings.

Discussion

- Spontaneous breathing established by this technique serves for desflurane elimination and provides opportunities of detecting abnormal respiratory patterns such as apneas and bradypnea possibly due to overdose of opioid. Furthermore, respiration after tracheal extubation was more stable with less abnormal breathing in hypercapnia patients.

- Consequently, we expect clinically significant advantages of this emergence method in patients anaesthetized with inhalation anesthetics.

- However, hypercapnia is not recommended for patients with intracranial diseases and severe cardiac and/or pulmonary comorbidities.

Discussion

- Desflurane elimination rate, which is theoretically determined by alveolar ventilation, cardiac output and desflurane diffusion.

- Under normal lung ventilation in hypercapnia patients, increased cardiac output during hypercapnia would more efficiently increase desflurane concentration gradients at both brain and lung.

- We would speculate that this would facilitate the local diffusion mechanisms due to the nature of the desflurane molecule with lower brain tissue-blood and blood-gas partition coefficients.

Discussion

- In addition, selective increase of cerebral blood flow relative to other organs in response to hypercapnia would further accelerate desflurane transport from the brain to lung.

- Therefore, our results strongly support involvement of higher cardiac output and selective increase of cerebral blood flow during hypercapnia as the mechanisms for facilitation of desflurane elimination during the shorter emergence period.

Limitations and unanswered questions to future research

- Firstly, the result of randomization was not blinded to the anesthesiologist. However, this potential bias was minimized by using spontaneous eye opening and ability to obey command as criteria for emergence from anesthesia.

- Secondly, participants were relatively young and healthy, and the results may differ in the different study populations, particularly in the elderly and patients with significant comorbidities.

Limitations and unanswered questions to future research

- Thirdly, we administered a small dose of propofol when cough occurred before cessation of desflurane (five patients in normocapnia group and four patients in hypercapnia group)

- and when desflurane inhalation was terminated to prevent emergence agitation, as this is a common clinical practice in our institute to prevent coughing and agitation during emergence from anesthesia.

Limitations and unanswered questions to future research

- Fourthly, ET-CO_2 achieved in the hypercapnia group (52 mmHg) was less than the originally targeted ET-CO_2 (60 mmHg) despite reduction of ventilator settings of respiratory rate and tidal volume.

- Lastly, this study was not designed to assess impact of hypercapnia on perioperative morbidity and mortality, length of hospital stay and health economics as clinical impact of intra-operative higher ET-CO_2 tested recently.

Critical Appraisal

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

Critical Appraisal

	Yes	Can't tell	No
2. Was the assignment of patients to treatments randomised?	✓		
3. Was the randomisation list concealed? Can you tell?			✓
4. Were all subjects who entered the trial accounted for at it's conclusion?			✓
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

Critical Appraisal

	Yes	Can't tell	No
6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?			✓
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

Critical Appraisal

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	-
10. How precise were the results? Were the results presented with confidence intervals?	yes

Critical Appraisal

	Yes	Can't tell	No
11. Do these results apply to my patient? • Is my patient so different from those in the trial that the results don't apply? • How great would the benefit of therapy be for my particular patient?	✓ ✓		
12. Are my patient's values and preferences satisfied by the intervention offered? • Do I have a clear assessment of my patient's values and preferences? • Are they met by this regimen and its potential consequences?			✓ ✓