Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial

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Summary

Background Risk factors for nosocomial pneumonia, such as gastro-oesophageal reflux and subsequent aspiration, can be reduced by semirecumbent body position in intensive-care patients. The objective of this study was to assess whether the incidence of nosocomial pneumonia can also be reduced by this measure.

Methods This trial was stopped after the planned interim analysis. 86 intubated and mechanically ventilated patients of one medical and one respiratory intensive-care unit at a tertiary-care university hospital were randomly assigned to semirecumbent (n=39) or supine (n=47) body position. The frequency of clinically suspected and microbiologically confirmed nosocomial pneumonia (clinical plus quantitative bacteriological criteria) was assessed in both groups. Body position was analysed together with known risk factors for nosocomial pneumonia.

Findings The frequency of clinically suspected nosocomial pneumonia was lower in the semirecumbent group than in the supine group (three of 39 [8%] *vs* 16 of 47 [34%]; 95% CI for difference 10·0–42·0, p=0·003). This was also true for microbiologically confirmed pneumonia (semirecumbent 2/39 [5%] *vs* supine 11/47 [23%]; 4·2–31·8, p=0·018). Supine body position (odds ratio 6·8 [1·7–26·7], p=0·006) and enteral nutrition (5·7 [1·5–22·8], p=0·013) were independent risk factors for nosocomial pneumonia and the frequency was highest for patients receiving enteral nutrition in the supine body position (14/28, 50%). Mechanical ventilation for 7 days or more (10·9 [3·0–40·4], p=0·001) and a Glasgow coma scale score of less than 9 were additional risk factors.

Interpretation The semirecumbent body position reduces frequency and risk of nosocomial pneumonia, especially in patients who receive enteral nutrition. The risk of nosocomial pneumonia is increased by long-duration mechanical ventilation and decreased consciousness.

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Introduction

Pneumonia is the most frequent nosocomial infection among intensive-care-unit (ICU) patients.[1] The frequency of nosocomial pneumonia in the ICU has been reported as between 9% and 70%, depending on the definition and the population studied.[2,3] Additionally, the incidence of nosocomial pneumonia varies among types of ICUs and ranges from 4·7 cases per 1000 ventilator days for paediatric ICUs to 35 cases per 1000 ventilator days in burn ICUs.[4,5] The incidence of nosocomial pneumonia in medical and surgical ICUs has been reported to range from 12·8 to 17·6 per 1000 ventilator days.[6] The recognised pathogenetic sequence of nosocomial pneumonia is abnormal oropharyngeal colonisation and subsequent aspiration. The colonisation of the oropharynx may be augmented by regurgitation of colonised gastric content. Colonisation of the stomach is favoured by the use of systemic or local antacid drugs and enteral nutrition, which alkalise gastric secretions and hence facilitate bacterial growth.[7] Although controversial, gastric reflux and subsequent aspiration to lower airways could play a part in the pathogenesis of nosocomial pneumonia.[8]

Two studies with radioactively labelled gastric contents showed that reflux can be reduced and subsequent aspiration avoided by positioning mechanically ventilated patients in a semirecumbent position.[8,9] In addition, an elevated head position (angle >30°) was also protective against nosocomial infection in an epidemiological study.[10] Although pneumonia was the most common nosocomial infection in that study, data on nosocomial pneumonia alone were not available. Kollef described in a cohort study a three-fold risk of nosocomial pneumonia, in patients with a supine head position during the first 24 h of mechanical ventilation.[11] Although the semirecumbent position has been strongly recommended by the US Centers for Disease Control and Prevention (CDC), the benefit for prevention of nosocomial pneumonia has never been proven in a randomised clinical trial.[4] We therefore investigated the frequency of nosocomial pneumonia in intubated and mechanically ventilated patients, randomly assigned to either supine or semirecumbent body positions.

Methods

Patients

Patients were recruited from June 1, 1997, until May 31, 1998, in the Hospital Clinic, a 1000-bed tertiary-care university hospital in two ICUs, a six-bed respiratory ICU, and eight-bed medical ICU.

All patients were routinely subjected to standard measures for general critical care and prevention of nosocomial pneumonia in mechanically ventilated patients, namely: sterile endotracheal suctioning; no change of mechanical ventilation tubing systems; stress ulcer prophylaxis with sucralfate (1 g every 4 h) given in patients who tolerated enteral feeding and intravenous ranitidine (50 mg every 6 h) or omeprazole (20 mg every 12 h) in patients receiving parenteral nutrition (in accordance with clinical

judgment, antacid medication was given in addition to sucralfate in some patients with present evidence or previous history of gastrointestinal bleeding).

Feeding was either parenteral or enteral depending on the decision of the physician in charge. Enteral feeding was continuous without rest period overnight and administered via two types of nasogastric tubes—small bore (2·85 mm, Flexiflow, Ross Laboratories, Columbus, OH, USA) and large bore (6·0 mm, Salam Sump, Sherwood Medical, Tullamore, Ireland). The composition of the enteral nutrition varied according to individual requirements and the total amount was calculated to provide 30–35 kcal/kg bodyweight per day. The initial delivery rate was 200 mL in 12 h and gastric aspiration was done every 4 h. The delivery rate was increased until individual requirements were met in the absence of problems associated with prolonged gastric emptying. The amount of enteral nutrition was within 1500–2000 mL per 24 h for all patients. Patients were classified as being on enteral nutrition if they had received at least 48 h of enteral feeding before pneumonia, extubation, or death.

A standard pressure area care protocol was followed in all patients, and a water-filled cushion was placed under the sacral region to minimise pressure. Selective digestive decontamination was not done in any patient. Surgical patients received perioperative antibiotic prophylaxis, if indicated.

Study design

The study consisted of three phases: start of the study protocol after patients had been intubated or admitted to the ICU; end of the study protocol with the first weaning trial, extubation, permanent change in body position for more than 45 min or death; follow-up for an additional 72 h. Surveillance for clinical detection of pneumonia was done daily. Samples for microbiological diagnostic tests were taken, if infection was clinically suspected. Exclusion criteria were: recent abdominal surgery (<7 days); recent neurosurgical interventon (<7 days); shock refractory to vasoactive drugs or volume therapy; previous endotracheal intubation (<30 days). The study was approved by the ethics committee and conducted in accordance with its guidelines.

Informed consent was obtained for all patients from the next-of-kin before randomisation. Patients were randomly allocated to either semirecumbent (45°) or supine body positon (0°) by a computer-generated list and all consecutive patients were included. The allocation table was generated and disclosed by an independent person. All medical care personnel were instructed not to change the position, unless for medical requirements—the correctness of the position was checked daily.

All relevant data from the patient's medical records and bedside flow charts were reviewed on admission to the ICU: age, sex, smoking habits (current smoker, ex-smoker [>2 years], and non-smokers), chronic alcohol abuse (>80 g alcohol per day), intravenous drug abuse, cause of respiratory failure, and severity of underlying medical disease (non-fatal, rapidly fatal, ultimately fatal). 8 h after ICU admission clinical data for calculation of the APACHE II score, the Glasgow coma scale, and the level of consciousness induced by sedation[12] were retrieved.

At the end of the protocol the following variables were recorded: duration of mechanical ventilation, duration and type of nasogastric intubation, nutrition, and stress ulcer prophylaxis; sedative treatment (any sedative agent given continuously for ⩾24 h), antimicrobial treatment (administered intravenously for ⩾24 h during the hospital stay), body position (according to definition), duration of hospital stay before ICU admission, length of ICU stay, comorbidities (cardiovascular disease, abnormal hepatic function, haematological diseases, polytrauma, diabetes mellitus, chronic obstructive pulmonary disease, malignant diseases, immunosuppression (corticosteroid treatment ⩾5 mg/day, HIV infection, chemotherapy within the previous 45 days, neutropenia (neutrophil count $\leqslant 5\times10^8$/L) or organ transplant recipient [kidney, liver, heart, or bone marrow] requiring immunosuppressive agents), and recent surgery.

Depending on the clinical situation a tracheobronchial aspirate, a protected specimen brush, or a bronchoalveolar lavage was done if pneumonia was suspected clinically. Tracheobronchial aspirate was collected without prior administration of saline in a standard sputum trap (Proclinics, Barcelona). For fiberoptic bronchoscopic examinations (Pentax FB18, Asahi Optical Ltd, Japan) patients were premedicated with propofol or midazolam. No local anaesthetics were administered and suction was avoided. Broncholaveolar lavage and protected specimen brush were done in the areas most prominently affected on chest radiograph or in one segment of the lower lobes in cases with diffuse infiltrates. Broncholaveolar lavage was done by instillation of three 50 mL volumes of non-bacteriostatic saline, and the first aspirated portion was discarded. Protected specimen brush (Mill-Rose Inc, 7310, Mentor, OH, USA) samples were retrieved as previously described.[13]

All samples were processed within 30 min. Samples were quantitatively plated on blood, chocolate, Wilkins-Chalgren and Sabouraud agar media in serial dilutions of 1 in 10, 1 in 100, and 1 in 1000. If negative, the plates were discharged after 3 days of testing for aerobic bacteria and after 4 weeks of testing for fungi. If positive, results were expressed as colony-forming units (cfu) per mL. Identification and susceptibility testing were done with standard methods. For purposes of analysis, only potentially pathogenic microorganisms were taken into account. The following microorganisms were excluded as non-pathogenic microorganisms: *Streptococci* spp except *Streptococcus pneumoniae*, coagulase-negative staphylococci, *Neisseria* spp, and *Candida* spp (thresholds of significant growth for pathogenic microorganisms were: 10^5 cfu/mL in tracheobronchial aspirate, 10^4 cfu/mL in bronchoalveolar lavage, and 10^3 cfu/mL in protected specimen brush cultures.[14,15]

Clinical suspicion of pneumonia was defined by new and persistent infiltrates on chest radiography most likely to be associated with pulmonary infection and at least two of the following three criteria: fever (temperature ⩾38·3°C); leucopenia or leucocytosis (white blood-cell count $\leqslant 4\times10^9$ or $\geqslant 12\times10^9$/L); purulent tracheal secretions. Nosocomial pneumonia was regarded as microbiologically confirmed in the presence of clinical suspicion of pneumonia and at least one pathogenic microorganism in tracheobronchial aspirate, bronchoalveolar lavage, or protected specimen brush, with bacterial growth above the defined thresholds for positive cultures of blood or pleural fluid, or both. The frequency of clinical and microbiologically confirmed nosocomial pneumonia was defined as number of cases per 100 patients and the rate was defined as the number of cases per 1000 ventilator days.

Statistical methods

The primary objective of this study was to assess the frequency of clinically suspected pneumonia in semirecumbent and supine body position. A secondary objective was to compare the frequency of microbiologically confirmed pneumonia in both study groups. Initial calculations showed a sample size of 182 patients to show a 50% risk reduction by the semirecumbent position (confidence level [1-α] 95%, power level 80% [1-β], projected frequency in the supine group was 40%). One planned interim analysis, comparing the frequency of the primary study objective between the two study groups was done after inclusion of 50% of the patients. A stochastic curtailment was used to correct for multiple analyses. The interim analysis revealed a significant reduction of the frequency of clinically suspected pneumonia in the semirecumbent position (p=0·003) and the trial was stopped.

For the univariate analyses, frequencies were compared by means of χ^2 test or Fisher's exact test, where appropriate. Means were compared by unpaired Student's *t* test, and corrected for inequality of variances (Levene's test). Adjusted odds ratios and 95% CI were computed for variables significantly associated with pneumonia.

In the analytical procedures, all categorical attributes (such as presence or absence of particular manfestations) were initially regarded as individual variables and dimensional variables (such as age or APACHE II score) were initially maintained in

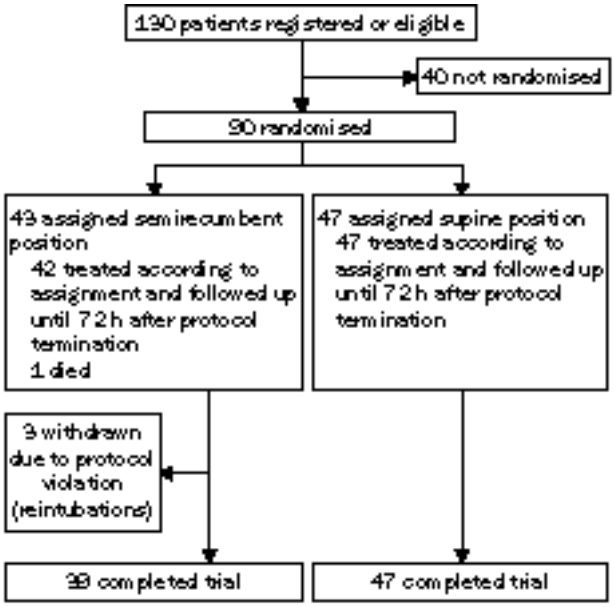

Figure 1: **Trial profile**

dimensional form. The variables were then tested for significant differences between study groups and the results were reported in the original form.

All risk factors tested in this analysis had been previously described for ICU patients. The factors included in further analyses were then divided into extrinsic and intrinsic risk factors. The reasons behind this procedure were to reduce the number of candidate variables and to separate factors that can be influenced by the physician (extrinsic, eg body position) from those that cannot (intrinsic, eg age). All dimensional variables were dichotomised with the use of cut-off points that were either consistent with previously published definitions (eg, coma defined as Glasgow coma scale score <9), important for the cause of pneumonia (eg, mechanical ventilation ⩾7 days), or in accordance with customary clinical judgment (eg, two or more comorbidities).

The following intrinsic risk factors of nosocomial pneumonia were tested: age (⩽65 years *vs* 65 years), mechanical ventilation (<7 days *vs* ⩾7 days), hospital admission before ICU admission (<48 h *vs* ⩾48 h), sex, APACHE II score on admission (<20 *vs* ⩾20), Glasgow coma scale score on admission (⩾9 *vs* <9), sedation score (<4 *vs* ⩾4), severity of the underlying disease (non-fatal *vs* fatal or ultimately fatal), number of comorbidities (one or none *vs* two or more), immunosuppression (not present *vs* present), and recent surgery. The following extrinsic risk factors were analysed: sedative medication, enteral nutrition, parenteral nutrition, bore of nasogastric tube (2·85 mm *vs* 6·0 mm), medication with sucralfate, ranitidine, or omeprazole, antibiotic medication for longer than 72 h, heated humidifiers, and supine body position.

For the multivariate analyses a logistic-regression analysis was done and precautions were taken to avoid common pitfalls associated with multivariable analysis.[16] Stringent entry criteria ($p<0·05$ in univariate analyses) and separate analysis of intrinsic and extrinsic risk factors reduced the number of candidate variables to avoid overfitting. To correct for colinearity, a conditional stepwise forward model was chosen ($p<0·05$). Interactions were analysed pairwise by entering an interaction term into the logistic-regression analysis. Results are reported separately when interaction was found ($p<0·05$).

The Kaplan-Meier method was used to display time-to-event data for clinically suspected pneumonia and death. Curves were compared by use of the log-rank test.

All data were processed with SPSS, version 7·5. Data are reported as counts or mean (SD) with the two-tailed level of significance.

Results

Patients

90 patients were randomly assigned with semirecumbent or supine body position (figure 1). Four patients were excluded from the analysis: one died during resuscitation 2 h after initiation of the protocol and three because of protocol violation (reintubated patients all in semirecumbent position).

A total of 86 patients (65 male and 21 female, mean age 65 years [SD15]) completed the clinical trial. Among the 86 patients the reasons for termination of the protocol were: change in position for more than 45 min (seven/86, 8%), death during the protocol (13/86, 15%), and weaning trial (66/86, 77%). Overall 39/86 patients were in the semirecumbent position (45%) and persistent supine position was maintained in 47/86 patients (55%). Table 1 compares general data of patients in supine and semirecumbent position. Patients in supine position tended to be less well, but the difference in APACHE II score was not significant.

Incidence of clinically suspected pneumonia

Pneumonia was clinically suspected in 19 of the 86 patients (22%) and could be microbiologically confirmed in 13 (15%); the incidence rate for the former was 28·7 per 1000 ventilator days and 19·6 per 1000 ventilator days for the latter. Table 2 summarises the microorganisms recovered.

Pneumonia was clinically suspected in three (8%) of 39 patients in the semirecumbent group and 16 (34%) of 47 in the supine group (95% CI for difference 10–42, p=0·003). Microbiologically confirmed pneumonia occurred in two (5%) patients in the semirecumbent

	Supine (n=47)	Semirecumbent (n=39)
Mean (SD) age (years)	67 (14)	63 (16)
Sex, male	35 (75%)	30 (77%)
Current or ex-smokers	32 (68%)	27 (69%)
Chronic alcohol abuse	9 (19%)	9 (23%)
Intravenous drug abusers	0	2 (5%)
Cause of acute respiratory failure		
Chronic obstructive pulmonary disease	16 (34%)	13 (33%)
Other pulmonary diseases	12 (26%)	8 (21%)
Surgery	6 (13%)	7 (18%)
Drug overdose or neurological emergency	3 (6%)	5 (13%)
Other	10 (21%)	6 (15%)
Severity of underlying disease		
Disease fatal or ultimately fatal	44 (94%)	31 (80%)
Mean (SD) APACHE II score	23·8 (6·1)	21·3 (6·0)
Mean (SD) Glasgow coma scale score	9·4 (4·3)	10·3 (4·2)
Duration of mechanical ventilation		
Mean (SD) total (h)	171 (167)	145 (149)
⩾7 days	18 (38%)	10 (26%)
Duration of ICU stay (days) mean (SD)	9·7 (7·8)	9·3 (7·2)
Heated humidifier	20 (43%)	17 (44%)
Large bore nasogastric tube	41 (87%)	28 (72%)
Enteral nutrition	28 (60%)	22 (56%)
Parenteral nutrition	10 (21%)	3 (8%)
Medication before protocol termination		
Sucralfate	35 (75%)	33 (85%)
Ranitidine	29 (62%)	16 (41%)
Omeprazole	6 (13%)	6 (15%)
Sedation	45 (96%)	37 (95%)
Antibiotic drugs	24 (51%)	18 (46%)

Table 1: **General data of patients in supine and semirecumbent position**

	Body position					
	Supine			Semirecumbent		
	TBAS	PSB	BAL	TBAS	PSB	BAL
Negative cultures	1	. .	. .	. .	. .	. .
Gram-negative organisms						
Acinetobacter spp	1	. .	. .	. .	. .	. .
Proteus spp	1	. .	. .	. .	. .	. .
Pseudomonas spp	2	3	. .	2	. .	1
Stenotrophomonas spp	. .	. .	. .	. .	. .	1
Gram-positive organisms						
Staphylococcus aureus (meticillin resistant)	2	3	1	. .	. .	. .
Staphylococcus aureus (meticillin sensitive)	2	1	. .	. .	. .	. .
Enterococcus spp	1	. .	. .	. .	. .	. .
Fungi						
Candida spp	1	. .	. .	. .	. .	. .
Total number of samples*	10	5	1	2	0	1

TBAS=tracheobronchial aspirate; PSB=protected specimen brush; BAL=bronchoalveolar lavage. Number of all recovered potentially pathogenic microorganisms without respect to the defined thresholds. In addition the following non-pathogenic microorganisms were recovered: *Streptococcus viridans* (n=1), *Chromobacter* spp (n=1).
*p=0·259, χ^2 test.

Table 2: **Microorganisms recovered on the day of clinical suspicion of pneumonia**

group and 11 (23%) in the supine group (95% CI for difference 4–33, p=0·018). The risk reduction was 76% for clinically suspected and 78% for microbiologically confirmed nosocomial pneumonia.

Most cases of clinically suspected pneumonia (15/19, 79%) or microbiologically confirmed nosocomial pneumonia (11/13, 85%) were of the late-onset type (mechanical ventilation ⩾96 h, table 3). There was a non-significant trend towards a longer duration of mechanical ventilation until pneumonia occurred in patients in the semirecumbent body position. Kaplan and Meier's analysis confirmed a significantly lower incidence of clinical suspicion of pneumonia in the patients in semirecumbent body position (figure 2). The incidence rate of clinically suspected pneumonia was lower in the semirecumbent group (10·9 per 1000 ventilator days) than in patients with supine body position (41·2 per 1000 ventilator days). The incidence rate of microbiologically confirmed pneumonia was 7·3 per 1000 ventilator days in semirecumbent and 28·4 per 1000 ventilator days in supine position.

Extrinsic risk factors of pneumonia

Clinically suspected pneumonia was associated in the univariate analysis with enteral nutrition and supine body position (table 4). Logistic-regression analysis showed enteral nutrition (adjusted odds ratio 5·7 [95% CI 1·5–22·8], p=0·013) and supine body position (6·8 [1·7–26·7], p=0·006) as independent risk factors of clinically suspected pneumonia.

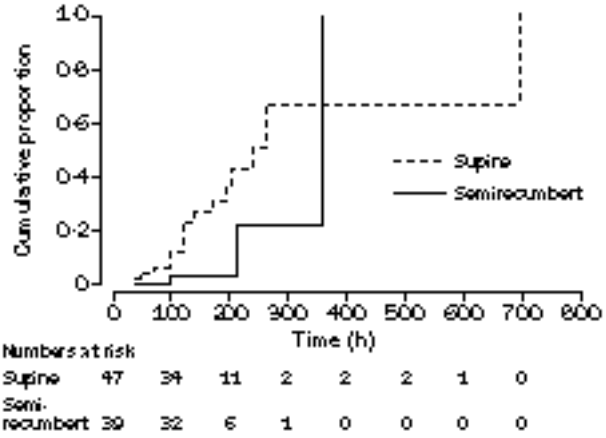

Figure 2: **Cumulative proportion of patients with clinically suspected pneumonia**
Comparison of semirecumbent and supine body position (log-rank test, p=0·018).

Microbiologically confirmed pneumonia was significantly associated with enteral nutrition and with supine body position (table 4). The multivariate analysis of microbiologically confirmed pneumonia revealed enteral nutrition (adjusted odds ratio 11·8 [1·4–98·5], p=0·022) and supine body position (6·1 [1·2–30·9], p=0·038) as independent risk factors.

Intrinsic risk factors of pneumonia

Mechanical ventilation for 7 days or more, an APACHE II score of 20 or greater a sedation score of 4 or greater, and a Glasgow coma scale of less than 9 were associated with clinical suspicion of pneumonia (table 5). Mechanical ventilation for 7 days or more (adjusted odds ratio 10·9 [3·0–40·4], p=0·001) and a Glasgow coma scale of less than 9 (4·0 [1·1–14·5], p=0·035) were independently associated with clinical suspicion of pneumonia in multivariate analysis.

Requirement for mechanical ventilation of 7 days or more, an APACHE II score of 20 or greater, and coma according to Glasgow coma scale of less than 9 were significantly associated with microbiologically confirmed pneumonia in the univariate analysis. The multivariate analysis showed only requirement for mechanical ventilation of 7 days or more (adjusted odds ratio 42·7 [5·2–354·0], p=0·001) as an independent factor associated with microbiologically confirmed pneumonia.

	Clinically suspected pneumonia (n=19)			Microbiologically confirmed pneumonia (n=13)		
	Supine (n=16)	Semirecumbent (n=3)	p (95% CI for difference)	Supine (n=11)	Semirecumbent (n=2)	p (95% CI for difference)
Mean (SD) age (years)	62·8 (15·5)	55·3 (19·7)	0·474 (−13·8 to 28·8)	58·7 (16·6)	44·0 (2·8)	0·254* (−6·9 to 36·3)
Mean (SD) APACHE II score	24·3 (5·7)	18·0 (5·2)	0·097 (−1·2 to 13·8)	24·8 (4·4)	20·0 (5·6)	0·119* (−2·9 to 12·5)
Duration of mechanical ventilation						
Mean (SD) until event (h)	166·3 (155·7)	222·0 (132·4)	0·571* (−147·6 to 259·0)	187·6 (180·8)	228·0 (186·6)	0·778* (−266·4 to 347·2)
Number with event in ⩾48 h	15 (94%)	3 (100%)	1·0† (−5·6 to 17·6)	11 (100%)	2 (100%)	1·0†‡
Number with event in ⩾96 h	12 (75%)	3 (100%)	1·0† (−3·8 to 46·2)	9 (82%)	2 (100%)	1·0† (−4·7 to 40·7)
Mean (SD) first weaning trial, death or extubation (h)	201·7 (178·9)	300·2 (140·1)	0·383* (−133·5 to 330·5)	246·3 (197·9)	345·3 (164·5)	0·523* (−231·1 to 429·1)
Mean (SD) duration of ICU stay, to discharge or death (h)	295·5 (212·5)	339·0 (118·8)	0·738* (−226·9 to 313·9)	369·0 (215·0)	377·0 (140·0)	0·961* (−346·1 to 362·1)

*Student's *t* test. †Fisher's exact test. ‡ CI cannot be computed.

Table 3: **Clinical characteristics of patients with clinically suspected pneumonia and microbiologically confirmed pneumonia with regard to body position**

	Clinical suspicion of pneumonia				Microbiologically confirmed pneumonia			
	Frequency of diagnosis	p	95% CI for difference	Odds ratio (95% CI)	Frequency of diagnosis	p	95% CI for difference	Odds ratio (95% CI)
Sedative medication								
Yes	17/82 (21%)	0·210*	−20·8 to 78·8	. .	11/82 (13%)	0·107*	−12·5 to 86·5	. .
No	2/4 (50%)				2/4 (50%)			
Enteral nutrition								
Yes	16/50 (32%)	0·009†	8·3 to 39·7	5·2 (1·3–24·8)	12/50 (24%)	0·007*	7·9 to 34·1	11·1 (1·4–239·2)
No	3/36 (8%)				1/36 (3%)			
Parenteral nutrition								
Yes	5/13 (39%)	0·150*	−8·0 to 48·0	. .	3/13 (23%)	0·406*	−15·2 to 33·2	. .
No	14/73 (19%)				10/73 (14%)			
Nasogastric tube size								
Large bore	3/17 (18%	0·753*	−15·8 to 25·8	. .	2/17 (12%)	1·0*	−13·7 to 21·7	. .
Small bore	16/69 (23%)				11/69 (16%)			
Sucralfate medication								
Yes	18/68 (27%)	0·063*	5·8 to 36·2	. .	13/68 (19%)	0·061*	9·7 to 28·3	. .
No	1/18 (6%)				0/18			
Ranitidine medication								
Yes	9/45 (20%)	0·624†	−13·4 to 21·4	. .	5/45 (11%)	0·277†	−7·1 to 23·1	. .
No	10/41 (24%)				8/41 (19%)			
Omeprazole medication								
Yes	4/12 (33%)	0·451*	−16·2 to 40·2	. .	3/12 (25%)	0·380*	−14·7 to 36·7	. .
No	15/73 (21%)				10/74 (14%)			
Antibiotic medication >72 h before event								
Yes	5/22 (23%)	1·0*	−19·3 to 21·3	. .	4/22 (18%)	0·732*	−14·2 to 22·2	. .
No	14/64 (22%)				9/64 (14%)			
Heated humidifier								
Yes	8/37 (22%)	0·927†	−17·7 to 17·7	. .	4/37 (11%)	0·333†	−7·7 to 21·7	. .
No	11/49 (22%)				9/49 (18%)			
Body position								
Supine	16/47 (34%)	0·003†	10·0 to 42·0	6·2 (1·5–29·7)	11/47 (23%)	0·018*	4·2 to 31·8	5·7 (1·1–39·9)
Semirecumbent	3/39 (8%)				2/39 (5%)			

Odds ratios with 95% CI are reported for all variables entered into multivariate analysis (p<0·05). *Fisher's exact test. †χ^2 test.

Table 4: **Univariate variable statistics for extrinsic risk factors of nosocomial pneumonia**

Analysis of interactions

Enteral feeding and body position showed a significant interaction in the analysis of clinically suspected pneumonia (adjusted odds ratio for the interaction term 10·6 [3·3–34·5], p<0·001). The frequency of clinically suspected pneumonia was highest when enteral feeding was given in supine body position (enteral feeding and supine body position 14/28, 50%; enteral feeding and semirecumbent body position two/22, 9%; no enteral feeding and supine body position two/19, 10%; no enteral feeding and semirecumbent body position one/17, 6%). In the analysis of intrinsic risk factors, mechanical ventilation of 7 days or more and coma according to the Glasgow coma scale also had a significant interaction term (11·8, 3·5–39·2, p<0·001). The frequency of clinically suspected pneumonia was highest when patients scored below 9 on the Glasgow coma scale and also required mechanical ventilation of 7 days or more (Glasgow coma scale score <9 and mechanical ventilation ⩾7 days 11/18; 61%; Glasgow coma scale <9 and mechanical ventilation <7 days three/15, 20%; Glasgow coma scale ⩾9 and mechanical ventilation <7 days four/10, 40%; Glasgow coma scale ⩾9 and mechanical ventilation <7 days one/43, 2%). In the analysis of microbiologically confirmed pneumonia the two extrinsic risk factors enteral nutrition and supine body position had also an significant interaction term (10·2 [2·5–41·1]; p=0·001). In accordance with the findings for clinically suspected pneumonia the interaction term was significant because the frequency of microbiologically confirmed pneumonia was highest when both risk factors were present (enteral feeding and supine body position ten/28, 36%; enteral feeding and semirecumbent body position two/22, 9%; no enteral feeding and supine body position one/19, 5%; no enteral feeding and semirecumbent body position zero/17).

Outcome

The overall mortality during the stay in the ICU was 20/86 (24%). The mean APACHE II score was 21·7 (SD 6·2) in survivors and 25·9 (4·7) in non-survivors (95% CI for difference 1·2–7·2, p=0·006). The length of mechanical ventilation until the end of the protocol did not differ significantly between survivors and non-survivors (108 [114] *vs* 131 [117] h [−35·2 to 81·2], p=0·430). The mean duration of ICU stay was 9·0 (7·4) days in survivors and 11·0 (8·0) days in non-survivors (1·8 to 5·8, p=0·315). Mortality in the ICU was seven/39 (18%) in the semirecumbent group and 13/47 (28%) in the supine group (−7·6 to 27·6, p=0·289), but also Kaplan-Meier statistics did not show a significant difference in survival between the two study groups (figure 3). Mortality was not significantly higher in patients with clinical suspicion of pneumonia compared with those without (six/19, 32% *vs* 14/67, 21%, −12·1 to 34·1, p=0·364). Accordingly, patients with microbiologically confirmed pneumonia tended to have a higher mortality, but this difference was also not statistically significant (five/13, 39% *vs* 15/73, 21%, 19·1 to 46·1, p=0·170).

Discussion

The pathogenesis of nosocomial pneumonia includes microaspiration to lower airways of abnormally colonised oropharyngeal or gastric contents, or both.[4] However, the role of the gastric reservoir for the pathogenesis of bacterial nosocomial pneumonia is controversial. Some studies found no clear sequence of colonisation from the stomach

	Clinical suspicion of pneumonia				Microbiologically confirmed pneumonia			
	Frequency of diagnosis	p	(95% CI)	Odds ratio (95% CI)	Frequency of diagnosis n	p	(95% CI)	Odds ratio (95% CI)
Age								
>65 years	10/45 (22%)	0·244†	−13·0 to 27·0	. .	5/55 (9%)	0·058*	−0·2 to 34·2	. .
≤65 years	9/31 (29%)				8/31 (26%)			
Mechanical ventilation								
≥7 days	15/28 (79%)	<0·001†	39·6 to 76·4	15·6 (3·9–67·8)	12/28 (43%)	<0·001†	22·3 to 59·7	48·9 (5·7–1092·9)
<7 days	4/58 (21%)				1/58 (2%)			
Hospitalisation before ICU admission								
≥48 h	6/30 (20%)	0·732†	−15·0 to 21·1	. .	5/30 (17%)	0·761*	−13·2 to 19·2	. .
<48 h	13/56 (23%)				8/56 (14%)			
Sex								
Female	5/21 (23%)	1·0*	−19·6 to 21·6	. .	3/21 (14%)	1·0†	−16·2 to 18·2	. .
Male	14/65 (22%)				10/65 (15%)			
APACHE II score								
≥20	17/53 (32%)	0·005†	11·1 to 40·9	7·3 (1·4–49·9)	12/53 (23%)	0·014*	7·3 to 32·7	9·4 (1·2–202·8)
<20	2/33 (6%)				1/33 (3%)			. .
Glasgow coma scale								
<9	14/33 (42%)	<0·001†	14·5 to 51·5	7·1 (2·0–26·5)	9/33 (27%)	0·027*	2·2 to 35·8	4·6 (1·1–20·0)
≥9	5/53 (9%)				4/53 (8%)			
Sedation score								
≥4	16/54 (30%)	0·029†	5·3 to 36·7	4·1 (1·0–19·5)	11/54 (20%)	0·119*	0·5 to 27·5	. .
<4	3/32 (9%)				2/32 (6%)			
Underlying disease								
Fatal	19/75 (25%)	0·112*	15·2 to 34·8	. .	13/75 (17%)	0·203*	8·5 to 25·5	. .
Not fatal	0/11				0/11			
Number of comorbidities								
≥2	18/70 (26%)	0·108*	4·5 to 35·5	. .	12/70 (17%)	0·446*	−3·6 to 25·6	. .
<2	1/16 (6%)				1/16 (6%)			
Immunosuppression								
Yes	6/29 (21%)	0·823†	−16·4 to 20·4	. .	4/29 (14%)	1·0*	−13·8 to 17·8	. .
No	13/57 (23%)				9/57 (16%)			
Recent surgery								
Yes	3/13 (23%)	1·0*	−23·8 to 25·8	. .	2/13 (15%)	1·0*	−21·1 to 21·1	
No	16/73 (22%)				11/73 (15%)			. .

The frequency of clinically suspected and microbiologically confirmed pneumonia in the presence and absence of each attribute are given together with the incidence in % and the univariable level of significance for this comparison. Odds ratios with 95% CI are reported for all variables entered into multivariable analysis (p<0·05). *Fisher's exact test. †χ^2 test.

Table 5: **Univariate variable statistics for extrinsic risk factors of nosocomial pneumonia**

to the pharynx or the airways,[17–19] whereas other studies provided clear evidence of the contributing role of the gastric reservoir to the pathogenesis of late-onset nosocomial pneumonia.[8,20,21] Gastro-oesophageal reflux is a consistent finding in mechanically ventilated patients and may favour pneumonia by promoting retrograde oropharyngeal colonisation and aspiration to lower airways. The presence of a nasogastric tube seems to be a key factor facilitating gastro-oesophageal reflux, owing to the compromised function of the lower oesophagus sphincter.[22]

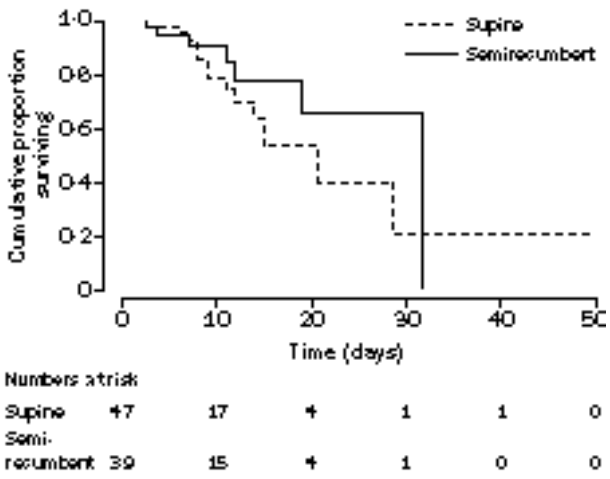

Figure 3: **Survival of patients in semirecumbent compared with supine body position**
Log-rank test, p=0·336.

We have clearly shown in our study that care of mechanically ventilated patients—with a nasogastric tube in place—in a supine body position increases the risk of nosocomial pneumonia. When patients were cared for in semirecumbent body position we observed more than 75% reduction of the rate of nosocomial pneumonia and the rate per 1000 ventilator days was reduced almost fourfold. In addition, we confirmed the increased risk of nosocomial pneumonia for patients in supine body position in a multivariate analysis together with enteral feeding, mechanical ventilation for 7 days or more, and coma on admission (Glasgow coma scale <9).

The mechanisms by which the semirecumbent position prevents nosocomial pneumonia are not fully understood. But the previous finding that this position decreases gastro-oesophageal reflux, abnormal oropharyngeal colonisation, and aspiration of gastric contents to lower airways supports the hypothesis that this measure prevents or at least slows the gastro-oropharyngeal route of pulmonary infection. This hypothesis is strongly supported by the analysis of interactions in our multivariate model, because 50% of all patients who received enteral feeding in the supine body position eventually developed clinical signs of pneumonia. Two previous studies showed that uncontrolled volume of enteral nutrition may promote gastro-oesophageal reflux[23] and that reflux in intubated patients receiving enteral

nutrition is increased by the supine body position.[24] Our study shows in a randomised clinical trial that a supine body position and continuous enteral feeding are independent risk factors also for nosocomial pneumonia, especially when they are combined. This finding again strengthens the suggested pathogenesis involving reflux and aspiration and reinforces the potential role of the gastric reservoir in the acquisition of nosocomial pneumonia. Enteral nutrients are alkaline and may—depending on the gastric acidity—favour bacterial colonisation of the stomach.[25]

There are additional factors, however, that increase gastro-oesophageal reflux and aspiration. Among these, the nasogastric tube, the intragastric pressure, and the type of antacid medication could have important roles. Because the placement of a nasogastric tube was indicated in all patients we cannot comment on its potential contribution to the risk of nosocomial pneumonia. However, we used two different bores of nasogastric tubes in a well-balanced proportion and found no association with the development of nosocomial pneumonia. Intragastric pressure was controlled in our study by an incremental feeding schedule and frequent gastric aspiration, so differences in intragastric pressure are unlikely to have biased our results. The role of antacid medication in the development of nosocomial pneumonia is controversial. Initial studies raised the suspicion that antacids could promote pneumonia but we could not confirm this idea in a randomised trial.[26] Our study cannot provide relevant evidence, because gastroprotective treatment was given according to guidelines and was not randomised.[4] In univariate analysis we even observed an increased risk of nosocomial pneumonia in the group of patients receiving sucralfate, but this risk is probably associated with enteral nutrition because these patients routinely received sucralfate.

Other additional risk factors for nosocomial pneumonia found in multivariate analyses deserve comment. Some risk factors such as the duration of mechanical ventilation ($\geq$7 days) are obvious and have been shown before.[27] Decreased consciousness has also been associated with a high incidence of nosocomial pneumonia,[28] and Ewig and colleagues showed a distinct bacterial pattern in these patients.[21] We observed a particularly high risk of nosocomial pneumonia in patients who had both risk factors. This finding can be explained by the fact that coma on admission facilitates aspiration and thus early-onset pneumonia, whereas long-duration mechanical ventilation increases the risk later on (late-onset pneumonia).[2]

We did not detect that morbidity or mortality decreased significantly when we cared for our patients in semirecumbent body position. By contrast, Kollef and colleagues showed that a supine body position during the first 24 h of mechanical ventilation was an independent risk factor of a poor prognosis in patients with nosocomial pneumonia.[11] However, effects of body position on mortality should be caused by the attributable mortality of nosocomial pneumonia. In our study we did not find any differences in mortality between patients with and without nosocomial pneumonia. Larger sample sizes are needed to prove this idea and a study would have to accept significant differences in the nosocomial pneumonia rate that in the end might not translate into outcome differences.

The initial diagnosis in this study was based on clinical criteria that may have missed patients with nosocomial pneumonia. However, the operational characteristics of this method are reasonable, as was shown in a study in which biopsy samples were taken immediately after death.[29] Since the diagnostic methods were similar in both study groups, a bias is unlikely. The study was stopped before the calculated sample size was reached, which may be interpreted as a potential limitation because the small sample size might have suppressed the identification of other independent risk factors. However, statistical precaution was taken to avoid premature interpretation of interim results, which was a clear advantage for patients in the semirecumbent body position. The interpretation of the APACHE II and the Glasgow coma scale scores may have been hampered by the time in which the former was obtained and the inclusion of sedated patients into the calculation of the latter. Patients in the supine position were slightly less well at baseline as shown by the APACHE II score and the proportion of patients with predicted fatal or ultimately fatal diseases. Although these differences were not significant, they may have influenced our results. However, both measures were included in the multivariate analysis and the bias should therefore be limited. A multivariate time-to-event analysis (eg, Cox proportional-hazards model) would have been desirable for this type of data, but most of the candidate variables did not satisfy assumptions necessary for this type of analysis. Enteral feeding was clearly a risk factor for nosocomial pneumonia but was continuous in our units. Other feeding schedules, which support reacidification of the stomach or increase control of the intragastric pressure, do not decrease significantly the risk of nosocomial pneumonia.[30] We did not observe any adverse effects of the semirecumbent body position in the patients included in this study. However, exclusion criteria applied, and protective measures for prevention of pressure ulcers, for example, were followed in our units.

The semirecumbent body position is a low-cost and easy-to-apply measure to reduce the risk of nosocomial pneumonia in mechanically ventilated patients, especially when patients are receiving continuous enteral feeding through a nasogastric tube. In addition, physicians should also be especially alert to the possibility of nosocomial pneumonia in patients who are comotose when admitted or intubated and consecutively require mechanical ventilation for 7 days or more

Contributors

Mitra A Drakulovic was responsible for protocol design, recruitment of patients, data entry into the database, and assisted with writing of the manuscript. Antoni Torres was the study co-ordinator, and was involved in the design of the protocol, as well as writing and revision of the paper. Torsten Thomas Bauer did statistical analyses and wrote the paper. Jose M Nicholas, Santiago Nogué, and Miquel Ferrer enrolled patients into the study.

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