Intensive Care Med (2014) 40:1679–1687
DOI 10.1007/s00134-014-3424-3

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Comparison of two repositioning schedules for the prevention of pressure ulcers in patients on mechanical ventilation with alternating pressure air mattresses

Received: 27 April 2014
Accepted: 24 July 2014
Published online: 5 September 2014

For the PUPPAS Trial Investigators.

Take-home message: A schedule of repositioning every 2 h was not superior to every 4 h to prevent pressure ulcers in ICU patients under mechanical ventilation and on modern support surfaces. However, it requires a higher nursing workload and increases the likelihood of an adverse effect.

Electronic supplementary material
The online version of this article (doi: 10.1007/s00134-014-3424-3) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* The objective was to compare the effectiveness of repositioning every 2 or 4 h for preventing pressure ulcer development in patients in intensive care unit under mechanical ventilation (MV).
Methods: This was a pragmatic, open-label randomized clinical trial in consecutive patients on an alternating pressure air mattress (APAM) requiring invasive MV for at least 24 h in a university hospital in Spain. Eligible participants were randomly assigned to groups for repositioning every 2 ($n = 165$) or 4 ($n = 164$) h. The primary outcome was the incidence of a pressure ulcer of at least grade II during ICU stay.
Results: A pressure ulcer of at least grade II developed in 10.3 % (17/165) of patients turned every 2 h versus 13.4 % (22/164) of those turned every 4 h (hazard ratio [HR] 0.89, 95 % confidence interval [CI] 0.46–1.71, $P = 0.73$). The composite end point of device-related adverse events was recorded in 47.9 versus 36.6 % (HR 1.50, CI 95 % 1.06–2.11, $P = 0.02$), unplanned extubation in 11.5 versus 6.7 % (HR 1.77, 95 % CI 0.84–3.75, $P = 0.13$), and endotracheal tube obstruction in 36.4 versus 30.5 %, respectively (HR 1.44, 95 % CI 0.98–2.12, $P = 0.065$). The median (interquartile range) daily nursing workload for manual repositioning was 21 (14–27) versus 11 min/patient (8–15) ($P < 0.001$).
Conclusions: A strategy aimed at increasing repositioning frequency (2 versus 4 h) in patients under MV and on an APAM did not reduce the incidence of pressure ulcers. However, it did increase device-related adverse events and daily nursing workload.

Keywords Mechanical ventilation · Pressure ulcer · Prevention · Clinical trial · Repositioning · Intensive care unit

Introduction

Critical care patients frequently develop pressure ulcers (PUs), with incidence rates reaching 29 % [1, 2]. PUs are associated with adverse health outcomes, increased treatment costs, and potential litigation awards [1–7]. The main PU prevention measures are the application of repositioning schedules and the use of appropriate support surfaces [1]. It used to be the current practice in intensive care units (ICUs) to turn patients every 2 h [8]. However, the introduction of pressure-reducing support surfaces, considered to exert similar preventive effects [9–11], has led to a reduction in this frequency over the past few decades [12–14] and to the proposal of a 4-hourly schedule as standard protocol [15, 16]. However, no randomized controlled clinical trial has been conducted to compare the efficacy and harm of different repositioning schedules to prevent PU development in patients on advanced pressure-redistribution surfaces. Research in this line has been called for by various authors and agencies, e.g., the Ontario Health Technology Advisory Committee, especially in the critical care setting [1, 17, 18]. Furthermore, insufficient data are available on the safety of repositioning in ICU patients and the potential risk of respiratory and/or hemodynamic instability, which is a relevant issue given the usual presence of intravenous lines, monitoring wires, ventilator tubes, and drainage catheters, among others [19].

With this background, we designed a clinical trial to study the benefits and adverse events associated with different turning schedules in ICU patients under mechanical ventilation (MV) and on a modern support surface. The primary objective of this study was to determine whether a 2-h turning regime is more effective than a 4-h turning regime to prevent a PU of at least grade II in unselected critical patients on APAMs and under MV for at least 24 h [20].

Methods

Study design

A pragmatic, single-site, open label, parallel group randomized controlled trial (pressure ulcer prevention by repositioning associated with support surfaces [PUPPAS]) was conducted in the two mixed ICUs of a university hospital in southern Spain. The study was conducted according to a pre-experimental protocol, which is available as electronic supplementary material (ESM). Informed written consent was obtained from the patients (or family members) for their participation in the trial, which was approved by the institutional review board of the hospital. Independent study monitors verified the source data in accordance with an established monitoring plan. This trial was registered with Clinicaltrials.gov, number NCT00847665.

Patients were enrolled between 24 and 48 h from the start of MV. Eligible patients were randomly assigned (1:1 ratio) to groups for turning every 2 or 4 h. Randomization was done in blocks of six in order to balance the number of patients in the two groups. The allocation of patients was concealed by using prenumbered opaque, sealed envelopes.

Study patients

Eligible patients comprised all critically ill adults with no PU at ICU admission who received invasive MV for at least 24 h between February 2009 and January 2011. Exclusion criteria were pregnancy; age less than 18 years; not being on an APAM (due to lack of availability); weight greater than 140 or less than 45 kg (as per APAM specifications); refusal of consent; MV for more than 48 h before enrolment in the study; and inclusion in a related trial. The ICU patients under MV who were not eligible for randomization were entered into a registry.

Study procedures

The patients were repositioned by nursing staff every 2 h (intervention group) or 4 h (control group) according to the following successively repeated turning sequence: first, left side with 30° tilt; second, supine with 30° elevation of the head end and the foot end of the bed; third, right side with 30° tilt. It was a systematic lateral turning every 2 or 4 h for the total duration of each period. In the participating ICUs, a ratio of one registered nurse for every two patients was maintained throughout the three nursing shifts/day. Repositioning schedules could be interrupted in cases of hemodynamic or respiratory instability (see below) or by the decision of the attending physician or patient. The same APAM type (Total Care Duo2®, Hill-Rom Inc, Bastesville, IN) was used in all cases. Standard sedoanalgesia consisted of fentanyl plus propofol or midazolam. The weaning protocol included the daily interruption of sedatives and spontaneous awakening trials [21].

Outcome measures

The primary end point was the occurrence of a new PU (at least grade II) at any anatomic site between enrolment in the study and ICU discharge. A grade II PU was defined as an abrasion or blister in accordance with the European Pressure Ulcer Advisory Panel (EPUAP) classification system [22]. The presence of a PU was evaluated by five study nurses (PU evaluators), who took part in a group

training program on PU recognition before the trial to maximize the consistency and interrater reliability of the data collection.

Secondary end points were the implementation rate of the assigned turning schedule, in-hospital mortality rate, ICU mortality rate, MV duration, and length of ICU stay.

Secondary safety end points were unplanned extubation [23]; ET obstruction [defined as clinical suspicion of ET obstruction by secretion requiring tracheal suctioning and isotonic saline (8 mL) instillation] [24]; loss or displacement of medical device (including central venous catheter, arterial catheter, and thoracic and abdominal drains); the composite end point of these device-related adverse events; the presence of atelectasis; reintubation within 48 h after extubation; ventilator-associated pneumonia [25]; cardiac arrest for any cause; turning-associated cardiac arrest; turning-associated hemodynamic instability (defined by arterial blood pressure less than 90 mmHg, heart rate less than 40 or greater than 130 beats/min, and unstable cardiac rhythm); and turning-associated respiratory instability (defined by respiratory rate greater than 35 breaths/min, peripheral oxygen saturation less than 90 % or partial pressure of oxygen in arterial blood less than 60 mmHg).

The associated nursing workload was also assessed, defined as the median min/day devoted to the turning.

Statistical analysis

Using conventional calculations for a fixed-sample design, a sample size of 165 per group was estimated to provide 80 % power at a 0.05 (two-sided) level of significance to detect an absolute risk reduction (ARR) of 10 % in PU onset, assuming that PUs would develop in 17 % of the control (4 h) group, based on previous studies and our own data [11, 26]. The primary analysis was performed according to a modified intention-to-treat principle (because a patient was excluded after randomization), and no interim analysis was planned.

Variables were summarized as frequencies and percentages, means and standard deviations (SDs), or medians and interquartile ranges (IQRs), as appropriate. Baseline characteristics were compared between the groups by using the chi-square test (or Fisher's exact test) and Student's t test (or Mann–Whitney U test) as appropriate (see table footnotes).

The primary outcome (incidence of PU of at least -grade II) was compared between the groups by using unadjusted Cox regression analysis, calculating hazard ratios (HRs), 95 % confidence intervals (CIs), and P values. The PU incidence density was computed per 1,000 patient-days on MV and per 1,000 patient-days of ICU stay. Multivariate Cox regression analyses were also performed that adjusted for the following covariates: acute physiology chronic health evaluation (APACHE) II score, female sex, type of admission (medical or surgical), percentage implementation of turning protocol, presence of anemia and diarrhea, and the albumin level at admission. Kaplan–Meier survival curves were constructed for the PU incidence during the first 60 days post-randomization as a function of the turning schedule, and the log-rank test was used to evaluate the statistical significance of the curves. Light's kappa (k-statistic) was employed to assess the agreement among the five observers (nurse researchers) and the bootstrap technique was used to calculate the 95 % CI. Secondary end points were compared by using unadjusted Cox regression analysis for binary end points and the Mann–Whitney U test for quantitative end points. Subgroup analyses were performed with the a priori hypothesis that the expected direction of effect of repositioning every 2 versus 4 h would be greater in those patients with PU development risk factors (female sex, turning, anemia, implementation less than 33 %, surgical admission, presence of diarrhea, hypoalbuminemia, APACHE II score at least 25 points, and age above 75 years). The Cox model also was used to examine potential intervention–subgroup interactions using intervention, subgroup, and intervention–subgroup interaction as covariates, with no formal adjustments for multiple comparisons. SPSS version 15.1 and R version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses. $P \leq 0.05$ was considered statistically significant, using two-sided tests.

Results

Recruitment and patient characteristics

During the study period, 512 ICU patients under MV were assessed for eligibility, yielding a final study sample of 330 patients (Fig. 1), who were randomly assigned to a 2-h repositioning group ($n = 165$) or 4-h group ($n = 165$). One patient in the 4-h group withdrew consent, leaving a final study sample of 329 patients. No significant differences were observed between the eligible non-randomized patients and the randomized patients in mean (SD) age [60.8 (14.9) versus 61.6 (14.8) years, respectively] or APACHE II score [23.5 (7.3) versus 23.5 (7.2) points]. The two intervention groups had comparable characteristics at baseline (Table 1).

The mean (SD) percentage implementation of the turning schedule was 60.46 (23.55) % for the 2-h group and 61.03 (22.36) % for the 4-h group. Out of the total number of repositionings, 44.1 (18.1) % were manually performed by the nursing staff in the 2-h group and 45.8 (19.9) % in the 4-h group. The implementation rate of the turning schedules and the reasons for their interruption within the first 28 days are reported in eTable 1 in the ESM.

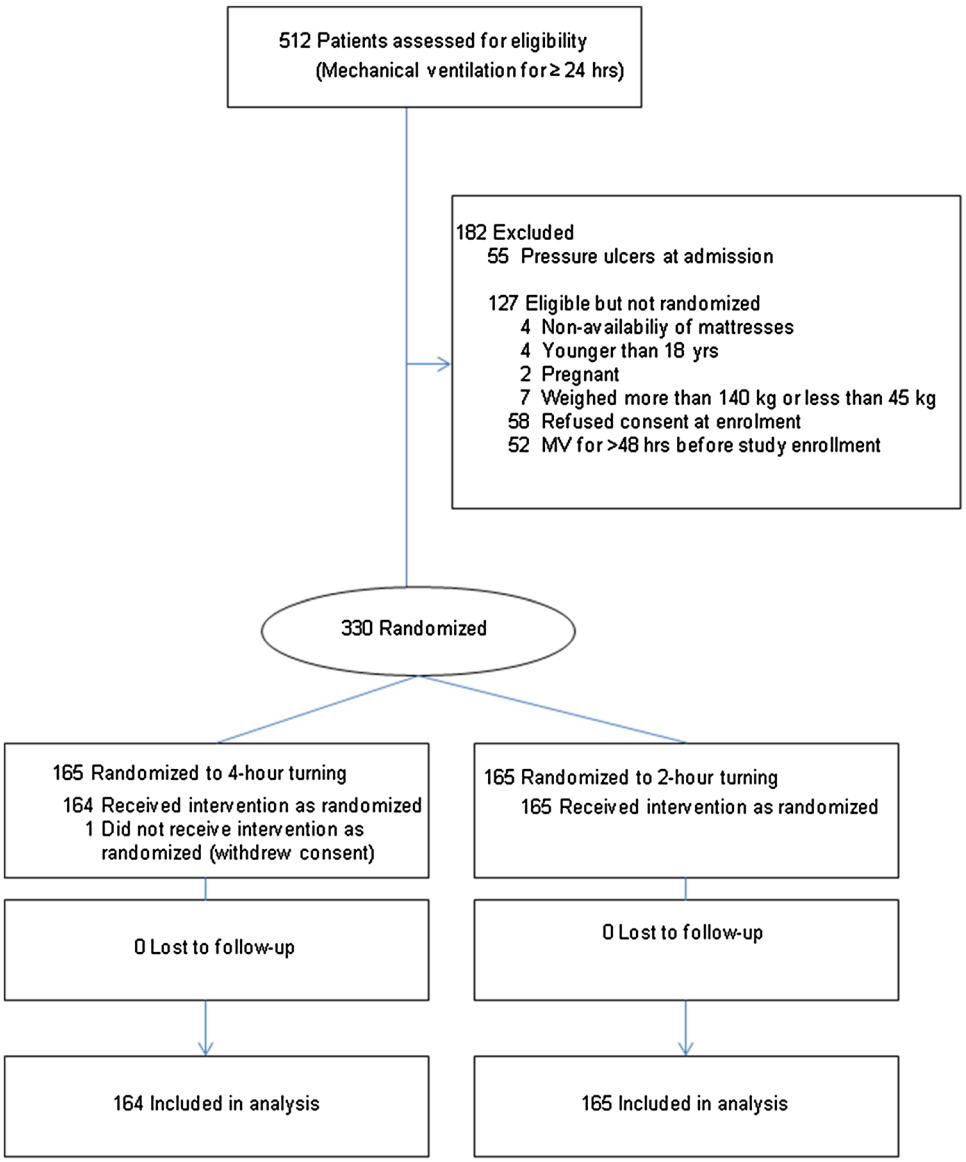

Fig. 1 Trial profile and flow of participants through the trial

Primary and secondary end points

PUs developed in 10.3 % (17/165) of the 2-h group versus 13.4 % (22/164) of the 4-h group (unadjusted HR 0.89, 95 % CI 0.46–1.71, $P = 0.73$) (Table 2). The PU incidence density per 1,000 days of ICU stay was 7.12 (17 cases/2,388 days, 95 % CI 4.15–11.4) in the 2-h group versus 8.93 cases (22 cases/2,462 days, 95 % CI 5.59–13.53) in the 4-h group ($P = 0.48$). The PU incidence density per 1,000 days on MV was 9.68 (17 cases/1,756 days, 95 % CI 5.6–15.5) in the 2-h group versus 12.12 cases (22 cases/1,815 days, 95 % CI 7.5–18.3) in the 4-h group ($P = 0.48$). Figure 2 depicts the Kaplan–Meier curve for the patients under MV for at least 24 h who did not develop a PU (at least grade II). After adjustment for the studied covariates, the Cox regression model yielded an adjusted HR for PU onset of 0.67 (95 % CI 0.33–1.16, $P = 0.27$) in the 2-h turning group with respect to the 4-h group (Table 3). A kappa value of 0.95 (95 % CI 0.91–0.98) was obtained for the inter-rater reliability of PU (at least grade II) detection by the five PU evaluators.

There were no differences in ICU mortality, hospital mortality, median MV duration, or length of ICU stay but the median (IQR) daily nursing workload was 21 (14–27) in the 2-h group versus 11 min/patient (8–15) in the 4-h group ($P < 0.001$) (see Table 2).

Adverse events

The composite end point of device-related adverse events was significantly more frequent (HR 1.50, CI 95 %

Table 1 Baseline demographics and clinical characteristics of study population

Characteristics	2-h turning ($n = 165$)	4-h turning ($n = 164$)	P value
Age, mean (SD), years	62.1 (14.5)	61.1 (15.1)	0.56
Sex, no. (%)			
Male	109 (66.1)	110 (67.1)	0.85
Female	56 (33.9)	54 (32.9)	
Origin, *n* (%)			
Emergency room	62 (37.6)	70 (42.7)	0.30
Hospital wards	30 (18.2)	38 (23.2)	
Surgery	57 (34.5)	44 (26.8)	
Other hospital	16 (9.7)	12 (7.3)	
Body mass index, mean (SD)[a]	27.8 (5.4)	27.8 (4.1)	0.98
Diabetes mellitus, *n* (%)			
No	123 (74.5)	123 (75)	0.92
Yes	42 (25.5)	41 (25)	
Pre-ICU LOS, mean (SD), days	2.84 (5.21)	3.45 (6.53)	0.35
Albumin at admission, mean (SD)	2.95 (0.68)	2.87 (0.58)	0.24
Braden scale, mean (SD), points	10.45 (1.13)	10.49 (1.02)	0.74
APACHE II score, mean (SD)[b]	23.4 (7.3)	23.5 (7.1)	0.87
Total SOFA on day 1, mean (SD)[c]	8.91 (3.63)	8.96 (3.49)	0.89
Cardiovascular SOFA	2.45 (1.80)	2.74 (1.76)	0.15
Respiratory SOFA	2.54 (0.87)	2.46 (0.73)	0.41
Renal SOFA	1.24 (1.32)	1.24 (1.42)	0.97
Type of admission, *n* (%)			
Medical	81 (49.1)	85 (51.8)	0.62
Surgical	84 (50.9)	79 (48.2)	
Reasons for MV, *n* (%)			
Neurological and trauma	13 (7.9)	19 (11.6)	0.38
Cardiac	26 (15.8)	33 (20.1)	
Respiratory failure	27 (16.4)	33 (20.1)	
Heart surgery	61 (37)	46 (28)	
Gastrointestinal	28 (17)	26 (15.9)	
Septic shock	10 (6.1)	7 (4.3)	
History of cancer, *n* (%)			
No	151 (91.5)	140 (85.4)	0.081
Yes	14 (8.5)	24 (14.6)	
Peripheral vascular disease, *n* (%)			
No	153 (92.7)	150 (91.5)	0.67
Yes	12 (7.3)	14 (8.5)	
Chronic renal failure, *n* (%)			
No	149 (90.3)	152 (92.7)	0.44
Yes	16 (9.7)	12 (7.3)	

SD standard deviation, *ICU* intensive care unit, *LOS* length of hospital stay, *APACHE* acute physiology and chronic health evaluation, *SOFA* sequential organ failure

[a] Body mass index is the weight in kilograms divided by the square of the height in meters

[b] The APACHE II score (range 0–71) is an index of the severity of illness; higher values indicate greater severity

[c] An index of the extent of organ failure in the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems (score range 0–24; higher values indicate greater severity of organ failure)

1.06–2.11, $P = 0.02$) in the 2-h group (47.9 %, 79/165) than in the 4-h group (36.6 %, 60/164). There were no differences in unplanned extubation and ET obstruction. Other data are shown in Table 2.

Subgroup analyses

No statistically significant differences were found in the subgroup analysis, assessing the effect modification by tests of interaction ($P > 0.05$) (eTable 2 in the ESM).

Discussion

This randomized trial was designed to reflect routine clinical care for an ICU patient on an APAM receiving MV for at least 24 h. The study hypothesis was rejected, because no difference in PU development was observed between patients turned every 2 h and those turned every 4 h. However, the study lacks sufficient statistical power to establish that clinically important differences are not present. By contrast, the frequency of a device-related adverse event was higher in the group that was more

Table 2 Clinical outcomes according to randomized study assignment

End point	2-h turning ($n = 165$)	4-h turning ($n = 164$)	Hazard ratio (95 % CI)	P value
Primary end point				
Pressure ulcer, *n* (%)	17 (10.3)	22 (13.4)	0.89 (0.46–1.71)	0.73
Secondary end points				
ICU mortality, *n* (%)	60 (36.4)	51 (31.1)	1.16 (0.80–1.69)	0.44
In-hospital mortality, *n* (%)	62 (37.6)	65 (39.6)	0.95 (0.67–1.36)	0.79
Length of ICU stay[a]	9 (5–21)	11 (7–21)		0.18
Duration of MV[a]	7 (3–15)	8 (5–15)		0.39
Workload of nurses, min/day[a]	21 (14–27)	11 (8–15)		<0.001
Secondary safety end point, *n* (%)				
Any device-related adverse event	79 (47.9)	60 (36.6)	1.50 (1.06–2.11)	0.02
Unplanned extubation	19 (11.5)	11 (6.7)	1.77 (0.84–3.75)	0.13
Endotracheal tube obstruction	60 (36.4)	50 (30.5)	1.44 (0.98–2.12)	0.065
Loss of medical devices	15 (9.1)	12 (7.3)	1.40 (0.64–3.08)	0.40
Reintubation[b]	12 (7.3)	7 (4.3)	1.94 (0.76–4.96)	0.17
Cardiac arrest for any cause[c]	6 (3.6)	10 (6.1)	0.63 (0.23–1.75)	0.38
Atelectasis	47 (28.5)	56 (34.1)	0.97 (0.65–1.44)	0.87
Respiratory instability	127 (77)	115 (70.1)	1.13 (0.88–1.47)	0.34
Hemodynamic instability	92 (55.8)	78 (47.6)	1.27 (0.93–1.73)	0.13
Clinical VAP	31 (18.3)	21 (12.8)	1.51 (0.85–2.65)	0.15

No data on primary and secondary outcomes were missing for any patients in the final sample

CI confidence interval, *ICU* intensive care unit, *MV* mechanical ventilation, *VAP* ventilator-associated pneumonia

[a] Continuous data are expressed as medians (interquartile range)

[b] Defined as reintubation within 48 h post-extubation

[c] There were no cases of cardiac arrest attributed to the repositioning in either group

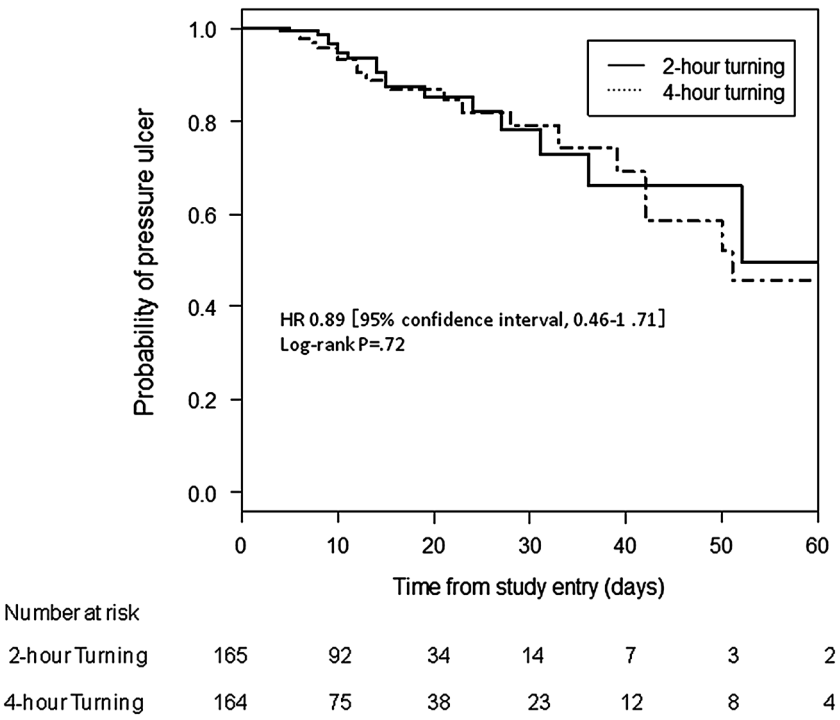

Fig. 2 Time-to-event curves for the primary end point (pressure ulcer of grade II or higher) during the first 60 days post-randomization. *HR* hazard ratio, *CI* confidence interval. Patients were censored at intensive care unit discharge and at death in the analyses

frequently turned. The higher turning schedule inevitably produced a significant increase in the nursing workload.

The present trial points towards that the more frequent turning of critical care patients who are on pressure-reducing mattresses does not necessarily lead to fewer PUs and cannot therefore be considered a more effective preventive measure. One explanation of this lack of effectiveness is that the implementation rate, may be more important than the repositioning schedule (every 2 or 4 h). In fact, if the turning implementation rate for each patient is considered independently of their group, a PU developed in less than 5 % of patients who received more

Table 3 Adjusted analysis of variables associated with developing a new pressure ulcer of grade II or higher in ventilated patients using Cox's model

	Hazard ratio (95 % CI)	*P* value
Turning group, 2-h turning	0.67 (0.33–1.16)	0.27
Implementation rate of turning schedule (%)	0.97 (0.95–0.98)	<0.001
APACHE II score, points	1.02 (0.97–1.07)	0.47
Type of admission, surgical	2.44 (1.14–5.23)	0.021
Diarrhea, yes[a]	1.87 (0.85–4.10)	0.12
Anemia, yes[b]	0.58 (0.22–1.53)	0.27
Sex, female	0.84 (0.42–1.68)	0.62
Albumin at admission (g/dL)	0.64 (0.35–1.20)	0.17

CI confidence interval, *APACHE* acute physiology and chronic health evaluation

[a] Diarrhea defined by 3 loose/liquid stools/day with a total volume greater than 250 mL/day during ICU stay

[b] Anemia defined by hemoglobin less than 8 g/dL during ICU stay

than 60 % of their scheduled turnings in comparison to around 20 % of those who received less than 33 % (eTable 1 in the ESM).

To the best of our knowledge, this is the first randomized trial on PU prevention that compares two turning strategies in adult ventilated ICU patients on a modern support surface such as the APAM. Only three previous studies analyzed the effect of repositioning on PU prevention in other (non-critical) patient populations and on less modern support surfaces [26–28]. None of them demonstrated that a higher turning frequency was more effective against PU development. A randomized study found that a 2-h turning schedule offered no improvement in PU incidence in comparison to a 4-h schedule (16.4 versus 21.2 %) in 235 residents of long-term care facilities on viscoelastic foam overlay mattresses [26]. Likewise, Moore et al. found no significant difference in the incidence of PUs of at least grade II in patients hospitalized in long-term care settings between those turned every 2 or every 4 h (2 versus 6 %) [27]. Finally, the results published by Defloor et al. are difficult to interpret, because they studied different repositioning schedules on various types of support surface [28].

Out of the 512 eligible patients, 330 (65 %) were enrolled in the study, which can be considered a high recruitment rate, supporting the external validity of the study [29]. The PU preventive measures [11] adopted by our center may explain the lower PU rate obtained in the patients receiving our routine ICU care (4-h turning schedule) in comparison to previous reports [9, 30], despite the inclusion of severely ill patients with high APACHE II and SOFA scores at ICU admission. Moreover, the median percentage implementation of turning schedules per patient (61 %) was considerably higher than has been observed by the few authors who measured this variable. Thus, Bours et al. reported that only 36.8 % of patients needing turning were receiving this treatment [13], while Özdemir and Karadag found that only 20–23.3 % of scheduled turnings were performed [31]. Furthermore, we adopted a conservative and safety-conscious approach to the turning schedules, which were interrupted whenever any hemodynamic or gas exchange alteration was detected, among other conditions in which repositioning was contraindicated [32, 33]. Further research is warranted to explore whether the compliance with turning regimens could be improved by increasing the administration of FiO_2 or using low doses of vasoactive drugs [34–36].

The present findings have important implications. First, a major reduction in nursing workload is obtained with a 4-h versus 2-h turning schedule. In addition, there are also advantages for the patients, including a reduced disturbance of their night rest. These benefits can be expected as long as patients are on pressure-reducing support surfaces at all times and receive a high level of standard care, as in the present study. Further advances in pressure-reducing support surfaces can be expected to deliver additional improvements in PU prevention, preferably at reasonable prices that allow their widespread utilization.

In relation to the limitations of the study, there is a risk of type II error (a false negative result), given that our study was powered to detect a 10 % absolute reduction in PUs, and a smaller difference may have gone undetected. In fact, the baseline risk (4-h turning) of a PU was almost 25 % lower than expected (13 versus 17 %), and the ARR was 3 % [relative risk reduction (RRR) of 23 %] in comparison to an estimated ARR of 10 % (RRR 41 %). Therefore, the results need to be replicated in an adequately powered trial before a positive effect of 2-h repositioning on PUs can be ruled out. A further limitation was the impossibility of blinding the nursing staff and the patients themselves to the turning schedule of the patients, increasing the risk of bias, although the five independent PU evaluators were blinded to the allocation of the patients. In addition, the results of our single-center study cannot be generalized to other ICUs with different training, infrastructures, or PU prevention protocols.

Some specific populations (e.g., traumatological and neurosurgical patients) were also poorly represented in our study population. There was no interim analysis, although a continuous system of vigilance was maintained through a committee established to monitor safety findings and intervene in the study if necessary on safety grounds. It was not possible to include a non-turning group in the trial for ethical reasons, given the nature of the present study population (non-selected ICU patients under MV for at least 24 h) [32, 33]. As our findings favored fewer repositionings, we could suggest that the next study should investigate no repositioning versus 4 h in the context of modern pressure air mattresses.

We conclude that the repositioning of mechanically ventilated patients every 2 h, which requires a higher nursing workload and increases the likelihood of an adverse effect, may offer no significant improvement in PU prevention, with the limitation that it has reduced statistical power. Nonetheless, it points to important outcomes of turning (safety and nursing workload). Future studies should be done to clarify the best repositioning schedule in this high-risk patient group, with the results of this trial as the basis.

Acknowledgments We acknowledge the efforts of the Data and Safety Monitoring Board members during the study: José Antonio Ramírez, Miguel Ángel Calleja, Manuela Expósito, Juana de Haro. We also acknowledge all the participants of PUPPAS Study Group: Susana Martínez, Raquel Álvarez-Jiménez, Alicia Jiménez-Pérez, Cristina Garrrido-Colmenero,Vanessa Muñoz, Rafael de la Chica, José Luís Pérez-Quirantes, Samuel Nievas, María Isabel Menéndez, Sonia Ortiz, María Ángeles Carvajal, Juan Alonso Cañadas, María Ángeles Calvo, Gertrudis Sanz, María Mar Marfil, M[a] Jesús Machado, Manuel González-Sandoval, Ana de Miguel, Carmen Robles, Ascensión Chamorro, Manuel Baena, María Cruz Medina, Trinidad Jiménez, Olga Erigaray, Mercedes Titos, Arancha González-espigares, Laura Millán, María Mar Aguilar, Juan Talavera, Lourdes Rodríguez, Antonio Escobar, María Dolores Cantero, Clara Rodríguez-Rodríguez, Pilar Toledano, and María Angustias Montijano.

Conflicts of interest The authors have not disclosed any potential conflicts of interest. This study was sponsored by grants from EFRD (European Fund for Regional Development) and the Spanish Institutes of Health Research (PI10/02923).

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