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ORIGINAL ARTICLE

Selective Digestive Tract Decontamination Decreases Time on Ventilator in Guillain–Barré Syndrome

Martine E. Bos Eyssen · Pieter A. van Doorn · Bart C. Jacobs · Ewout W. Steyerberg · Peter H. J. van der Voort · Durk F. Zandstra · Janneke Horn · Peter E. Spronk · Cornelia W. Hoedemaekers · Jan Bakker · Mathieu van der Jagt

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Abstract
Background Ventilator-associated pneumonia (VAP) occurs in more than half of mechanically ventilated patients with Guillain–Barré syndrome (GBS) and is associated with prolonged mechanical ventilation (MV). We investigated the impact of selective decontamination of the digestive tract (SDD), an intervention that reduces hospital acquired infections in ICU patients, on duration of MV in GBS and neurological outcome at 6 months.
Methods We performed a retrospective study in mechanically ventilated GBS patients in the Netherlands. We compared patients treated with and without SDD. Main outcomes were duration of MV and the ability to walk independently at 6 months. Statistical comparison was done with logistic and ordinal regression analyses.
Results We included 124 GBS patients on MV at 2 weeks after first symptoms (SDD, $n = 54$ and non-SDD, $n = 70$). The median duration of MV without SDD was 42 days (interquartile range, IQR 25–77 days) versus 29 days with SDD (IQR 17–45 days). Median duration of MV for all included patients was 35 days. The adjusted odds ratio (OR) for duration of MV $>$ 35 days in the SDD versus the

M. E. Bos Eyssen · P. A. van Doorn · B. C. Jacobs
Department of Neurology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands
e-mail: m.boseyssen@erasmusmc.nl

P. A. van Doorn
e-mail: p.a.vandoorn@erasmusmc.nl

B. C. Jacobs
e-mail: b.jacobs@erasmusmc.nl

B. C. Jacobs
Department of Immunology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

E. W. Steyerberg
Department of Public Health, Erasmus MC-University Medical Center, Rotterdam, The Netherlands
e-mail: e.steyerberg@erasmusmc.nl

P. H. J. van der Voort · D. F. Zandstra
Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
e-mail: P.H.J.vanderVoort@olvg.nl

D. F. Zandstra
e-mail: d.f.zandstra@olvg.nl

J. Horn
Department of Intensive Care, Academic Medical Center, Amsterdam, The Netherlands
e-mail: j.horn@amc.nl

P. E. Spronk
Department of Intensive Care, Gelre Hospital, Apeldoorn, The Netherlands
e-mail: p.spronk@gelre.nl

C. W. Hoedemaekers
Department of Intensive Care, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
e-mail: c.hoedemaekers@ic.umcn.nl

J. Bakker · M. van der Jagt (✉)
Department of Intensive Care, Erasmus MC-University Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
e-mail: m.vanderjagt@erasmusmc.nl

J. Bakker
e-mail: jan.bakker@erasmusmc.nl

non-SDD cohort was 0.37 (95% CI 0.17–0.77). SDD did not affect neurological recovery after 6 months from first symptoms. VAP occurred in 12% (95% CI 2–22%) in the SDD cohort and in 47% (95% CI 35–59%) in the non-SDD cohort.

Conclusions SDD in mechanically ventilated GBS patients reduced the time on the ventilator, probably by preventing VAP, but did not affect neurological recovery after 6 months.

Keywords Guillain–Barré syndrome · SDD · Mechanical ventilation · Ventilator-associated pneumonia · Prognosis

Introduction

Mechanical ventilation (MV) is required in 20–30% of patients with Guillain–Barré syndrome (GBS) [1, 2]. Ventilator-associated pneumonia (VAP) has been reported in 56–78% of mechanically ventilated GBS patients and is associated with prolonged MV [2–4]. Prolonged MV has been associated with delayed neurological recovery [1]. Selective decontamination of the digestive tract (SDD) has been shown to prevent VAP and other infections and decrease mortality in the critically ill [5, 6]. SDD is an infection–prophylaxis strategy which aims to eradicate potentially pathogenic aerobic bacilli causing nosocomial infections [7]. In GBS patients, infection prevention by SDD may have a beneficial impact on inflammation and thereby improve neurological recovery or reduce secondary deterioration, such as treatment related fluctuation (TRF) [8]. Moreover, shorter duration of MV may be associated with less additional ICU acquired weakness often seen in critically ill patients during extended periods of MV [9]. However, the impact of SDD on neurological recovery and duration of MV has not been investigated in GBS patients.

Therefore, we studied whether SDD had an impact on the duration of MV in GBS patients and on their neurological recovery.

Methods

We performed a multicenter retrospective cohort study in the Netherlands. To assess the effect of SDD, two cohorts were compared: (1) a cohort of GBS patients treated in ICUs were SDD was standard care for all patients on MV. Data for these patients were collected both from prospective and retrospective databases from previous observational studies and clinical trials [8, 10–13]. In addition, a retrospective survey was conducted among the ICUs where SDD was standard care and medical records of previously treated GBS patients were collected and data were extracted during site visits after obtaining permission from the ICU physicians, (2) a cohort of mechanically ventilated patients from ICUs where SDD was not applied routinely. Data for these patients were collected from prospective databases from previous trials [13, 14]. During the study period a minority of ICUs in the Netherlands applied SDD routinely, which gave us the unique opportunity to study whether mechanically ventilated GBS patients treated at these ICUs had different outcomes than those treated at ICUs where SDD was not applied routinely. The ethics committee of the Erasmus Medical Center approved the study and waived informed consent. Similar inclusion criteria were used as in previous studies [8, 10–14]: fulfillment of the diagnostic criteria for GBS [15] and onset of weakness less than 2 weeks prior to inclusion in the trials [16]. Only patients receiving MV at week 2 after disease onset were included. Exclusion criteria were: age <18 years, previous episode of GBS, pregnancy and having severe concurrent disease limiting short term prognosis.

The following data were obtained from all patients: age, preceding diarrhea, duration of MV, VAP, GBS disability score [17] at study entry and 6 months, and time to independent walking. These data were obtained from the prospective registers [8, 10–14] or by chart review and when necessary by telephone from either the patient's neurologist or rehabilitation physician. Other variables, such as days on ICU were not available from the prospective databases.

Main outcomes were duration of MV from the moment of inclusion in our study and the ability to walk independently at 6 months after onset of weakness. Secondary outcome was the incidence of VAP. We assessed whether pneumonia was documented both in the SDD and non-SDD cohort by means of retrospective chart review.

Statistics

To estimate the effect of SDD with regard to *neurological outcome at 6 months*, we adjusted for variables used to calculate the Erasmus Guillain–Barré Outcome Score (EGOS), a prognostic score with regard to chance of walking independently at 6 months, in multivariable analyses [16]. The EGOS is calculated using the following variables: age, preceding diarrhea and the GBS disability score [17] at week 2. GBS disability score was by definition 5 (MV at 2 weeks) in all included patients. Therefore, we used SDD, age and preceding diarrhea as covariables for multivariable ordinal logistic regression analysis to assess outcome at 6 months with GBS disability score as outcome variable. For the analyses, age was included as a continuous variable. We performed multivariable logistic regression with stepwise backward likelihood ratio analysis

to determine odds ratios for *duration of MV >35 days*. This cut-off point was chosen because it was the median duration of MV of all included patients. A stepwise method to select independent prognostic variables was chosen because variables predicting duration of MV in GBS have not been investigated. We included the following variables: treatment with SDD, diarrhea, age, time period (before 1990, 1991–2000, 2001 or later), type of hospital (academic vs. non-academic), treatment modality (plasma exchange [PE], intravenous immunoglobulin [IvIg], or IvIg + methylprednisolone [MP]). Differences between both cohorts in the incidence of pneumonia and baseline characteristics were tested with Pearson's chi-square test or Fisher's exact test.

Results

Time Periods and Baseline Data

We included 124 patients in the study, of whom 54 patients received SDD, and 70 patients were not treated with SDD (SDD cohort: retrospective $n = 37$, prospective $n = 17$). In the SDD cohort, patients were included between 1990 and 2008 (Table 1). In this cohort, data from 26 patients originated from previous prospective and retrospective studies [8, 10–13] and data from the other 28 GBS patients were collected for this study during site visits and chart reviews (these patients were admitted between 2003 and 2008). The non-SDD cohort consisted of patients included in prospective trials [13, 14] between 1986 and 2000 (Table 1). Among patients who received SDD ($n = 54$), less patients were admitted to an academic hospital ($n = 12$) than to a non-academic hospital ($n = 42$). In contrast, in the non-SDD cohort ($n = 70$), 50 patients were admitted to an academic hospital and 20 to a non-academic hospital (Table 1).

Table 1 Baseline data

	SDD cohort (%)	Non-SDD cohort (%)	*P* value
n	54	70	
Age (years)			
≤40	13 (24)	22 (40)	0.56*
41–60	18 (33)	24 (30)	
>60	23 (43)	24 (30)	
Diarrhea			
No	37 (69)	52 (74)	0.48
Yes	17 (31)	18 (26)	
Hospital			
Academic	12 (22)	50 (71)	<0.001
Non-academic	42 (78)	20 (29)	
Time period			
≤1990	2 (4)	42 (60)	<0.001
1991–2000	20 (37)	28 (40)	
>2000	32 (59)	0	

* Pearson's chi-square

The median age of the non-SDD cohort was 56 years and of the SDD cohort 54 years. There were no significant differences in age groups according to the EGOS between the cohorts. Incidence of diarrhea prior to onset of symptoms of GBS was similar in both cohorts (31% in the SDD cohort and 26% in the non-SDD cohort, $P = 0.48$; Table 1). The median EGOS in the non-SDD cohort at 2 weeks (baseline) was slightly more favorable than in the SDD cohort (5.75 vs. 6.0).

Clinical Course and Outcome

Five patients who were assessed for eligibility were already excluded from the above mentioned SDD cohort because of sepsis at the time of admittance to the hospital, AIDS, transition of diagnosis to Bickerstaff encephalitis, or because follow up data after ICU stay were not available. Also in the non-SDD cohort patients with severe concurrent disease limiting short term prognosis were excluded. One patient in the non-SDD cohort and three in the SDD cohort died during MV; in addition, three patients in the non-SDD cohort died after liberation from MV, but within 6 months. These patients were included in the analysis. Causes of death in the SDD cohort were: bowel ischemia, severe residual weakness after 6 months in combination with old age, and unclear cause of death. The causes of death of the patients who died in the non-SDD cohort are unknown. In both the SDD group and the non-SDD group, the percentage of patients who were able to walk independently *within* 6 months (GBS disability score ≤2 at 6 months) was 50% (27/54 and 35/70). In these patients ($n = 62$), the median time to independent ambulation in the SDD cohort was 85 days ($n = 27$) and in the non-SDD cohort 98 days ($n = 35$). The mean time to independent ambulation in the SDD cohort was 92 days (95% CI 75–104 days) and in the non-SDD cohort 90 days (95% CI 76–108 days).

Impact of SDD

The median duration of MV without SDD was 42 days (interquartile range, IQR 25–77 days) versus 29 days with SDD (IQR 17–45 days), Mann–Whitney *U* test, $P < 0.01$ (Fig. 1). In the stepwise logistic regression model, all variables, except SDD, were excluded because of non-significance, including type of hospital (academic vs. non-academic) and time period (Table 2). The odds ratio (OR) for duration of MV more than 35 days in the SDD versus

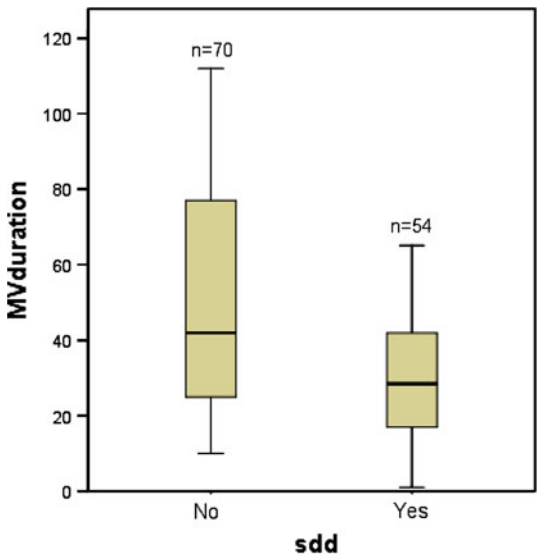

Fig. 1 Boxplot: Duration of mechanical ventilation in days without or with SDD in GBS patients

the non-SDD cohort was 0.37 (95% CI 0.17–0.77; Table 2). In multivariable ordinal logistic regression analysis, with GBS disability score at 6 months as the outcome variable, preceding diarrhea and age but not SDD were significantly associated with a higher GBS disability score at 6 months (diarrhea when present associated with 1.04 point GBS disability score increase, 95% CI 0.32–1.76, $P < 0.01$ and age per year 0.02 point GBS disability score increase, 95% CI 0.00–0.04, $P < 0.05$; Table 2). The results of the analyses of variables predicting the main outcomes (MV duration and GBS disability score at 6 months) did not change when performed after exclusion of the patients who died.

In a subset of 41 patients from the SDD cohort for whom these data were available (Refs. [8, 10, 13] and the retrospective survey), VAP occurred in only 5 patients (12%, 95% CI 2–22%; Table 3). From 13 patients in the SDD cohort [11, 12] data on pneumonia were not available. In the non-SDD cohort VAP occurred in 33 out of 70 patients (47%, 95% CI 35–59%). Mortality was not different between both cohorts (Table 3).

Discussion

SDD treatment of GBS patients who were mechanically ventilated at 2 weeks after onset of weakness significantly reduced the time spent on MV. The explanation for this finding seems to be a reduction in the incidence of pneumonia during MV by SDD from 47 to 12%. However, SDD treatment did not improve neurological outcome with regard to chance of independent walking at 6 months. SDD did also not result in reduced time to ambulation in patients who were able to walk independently within 6 months.

Some methodological issues need to be addressed. First, the combination of prospectively and retrospectively collected data made it possible to study as many patients as possible nationwide of a rare disease such as GBS and with patients who were mechanically ventilated and exposed to SDD, a treatment that is not applied at every ICU. Since patient data were collected from different sources, the time period during which the patients were included differed between the SDD and the non-SDD group. Second, potentially important details on ICU complications and pulmonary comorbidity that may have influenced the duration of MV in this group of patients were not available. However, the occurrence of ICU complications, among

Table 2 Main outcomes of regression analyses to assess effect of SDD on duration of mechanical ventilation and GBS disability score at 6 months

Analysis	Outcome	Covariable	Statistic (95% CI)	*P* value
Binary logistic regression[a]	MV >35 days	SDD	OR: 0.37 (0.17–0.77)	<0.01
Ordinal logistic regression	GBS disability score (at 6 months)	SDD	0.02 (−0.62 to 0.66)[b]	0.95
		Age	0.02 (0.0001–0.04)	<0.05
		Diarrhea	1.04 (0.32–1.76)	<0.01

MV mechanical ventilation, *SDD* selective decontamination of the digestive tract, *OR* odds ratio, *IvIg* intravenous immunoglobulin, *PE* plasma exchange, *MP* methylprednisolone

[a] Logistic regression with stepwise backward (likelihood ratio) selection of variables: included in model are SDD, diarrhea, age, time period, type of hospital, type of treatment (IvIg, PE, MP)

[b] Numbers represent change in GBS disability score associated with 1-point change of covariable

Table 3 Ventilator-associated pneumonia (VAP) and mortality

	SDD cohort (%)	Non-SDD cohort (%)	*P* value
VAP	$n = 41$	$n = 70$	
No	36 (88)	37 (53)	<0.001*
Yes	5 (12)	33 (47)	
Death <6 months	$n = 54$	$n = 70$	
No	51 (94)	66 (94)	NS**
Yes	3 (6)	4 (6)	

* Pearson's chi-square = 14.03 (df = 1)

** Fisher's exact test

which pneumonia is an important one, has been associated with increased time to ambulation [1]. Therefore, it seems reasonable to assume that the lack of difference in neurological recovery of patients over time in both cohorts suggests that important differences in ICU complications and comorbidity between cohorts were not very likely. Furthermore, in spite of the fact that the strong effect of SDD on duration of MV may be confounded by type of hospital (academic vs. non-academic) or the time period of treatment at the ICU, these variables were excluded by the stepwise regression model. Therefore, it is unlikely that time period or type of hospital had an important confounding effect on duration of MV in this study. Third, although prognostic factors for outcome at 6 months have been well validated in GBS [16], data on prognostic factors for duration of MV in GBS have not been studied previously. We used validated prognostic factors (age, preceding diarrhea, and GBS disability score at 2 weeks) to predict neurological recovery at 6 months (EGOS [16]) as covariables in regression analyses, to adjust for differences in entry characteristics. Because these factors predict the chance of ambulation at 6 months, they are possibly predictive for recovery of respiratory muscle strength as well and therefore it seems reasonable to adjust for these factors. However, we cannot exclude that other clinical variables, for instance autonomic dysfunction, axonal versus demyelinating nerve involvement or facial weakness that have been shown to predict the need for MV [18], may also be important for prediction of duration of mechanical ventilatory support. Although ICU complications such as pneumonia were not included in the EGOS, it is important to note that the EGOS had excellent validity for the chance to determine the recovery to independent walking at 6 months in a large cohort of patients with GBS [16].

Although data on the incidence of pneumonia was available for only 41 of the 54 SDD patients the incidence of pneumonia was significantly lower than in the non-SDD group and than previously reported [2, 3]. We have no reason to presume that in the 13 patients in whom data on pneumonia were unavailable, the incidence on VAP would be much higher. The lack of difference in neurological recovery of patients over time in both cohorts suggests that important differences in ICU complications and comorbidity between the cohorts did not occur. Our findings are in agreement with the expected effect of SDD, namely prevention of infections, especially VAP, in ICU patients, and corroborate the previously reported association between reduction of pneumonia and decreased duration of MV [3]. Although SDD as a prophylactic antibiotic regimen is still regarded by many as controversial because of concerns of selection of resistant bacteria, one of the largest studies to date from the Netherlands does not support introduction of antibiotic resistance in the short term [6]. Despite extensive interest in SDD, reported effects on patient outcome have been conflicting. On the other hand, it is conceptually valuable to study whether the prevention of VAP, for instance by SDD, in mechanically ventilated GBS patients may improve neurologic recovery. To our knowledge, this is the first study with the primary aim to assess the effect of SDD in GBS patients who are mechanically ventilated. In two previous retrospective studies the median duration of MV in GBS patients was 28 and 40 days [1, 3]. This is comparable to our findings of a median duration of MV of 42 days in the non-SDD versus 29 days in the SDD cohort. All patients in the non-SDD cohort and part of the patients in the SDD cohort in our study were extracted from a prospective registry whereas the two previous studies used only retrospectively collected data.

Shorter duration of MV and prevention of infections is not only intuitively beneficial. In ICU patients, VAP is associated with prolonged ICU length of stay [4] and in these patients SDD has been shown to reduce respiratory tract infections and mortality [19]. Moreover, studies have shown that prolonged MV was associated with major morbidity, pulmonary infections and increased mortality in GBS patients [20–22]. Unfortunately we were unable to study morbidity as data on morbidity, except pneumonia which data we retrieved by chart review, was not included in the prospective databases that most of our data originated from.

Conclusions

Our results suggest that SDD decreased the duration of MV in GBS patients. No indication of harmful effects of SDD was found in the context of this study. We did not find a positive effect of SDD on neurological recovery up to 6 months after first symptoms, but this may be due to the limited number of patients included or to the fact that recovery from GBS is primarily determined by other

factors. Because of the retrospective design of this study the positive results of SDD on the duration of MV should be regarded preliminary. Factors influencing the duration of MV in GBS should be further assessed in a prospective study, including SDD as a prognostic variable.

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