Journal of Clinical Virology 60 (2014) 215–221

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Is acyclovir effective among critically ill patients with herpes simplex in the respiratory tract?

Stephanie Traen[a,1], Niels Bochanen[a,1], Margareta Ieven[b], Tom Schepens[a], Peggy Bruynseels[b,2], Walter Verbrugghe[a], Philippe G. Jorens[a,*]

[a] Department of Critical Care Medicine, Antwerp University Hospital (UZA), University of Antwerp, Edegem, Belgium
[b] Department of Microbiology, Antwerp University Hospital (UZA), University of Antwerp, Edegem, Belgium

ARTICLE INFO

Article history:
Received 14 February 2014
Received in revised form 1 April 2014
Accepted 10 April 2014

Keywords:
Herpes
Critical care
Respiratory tract
Bronchoalveolar
Acyclovir
Outcome

ABSTRACT

Background and objective: The relevance of the detection of herpes simplex virus type 1 (HSV-1) in the respiratory tract of patients in the intensive care unit (ICU) is unclear. Therefore, it is uncertain whether treatment with an antiviral agent could be beneficial for these patients.
Study design: We retrospectively reviewed the records of ICU patients with a positive HSV-1 culture in the respiratory tract or bronchoalveolar lavage (BAL) fluid. We evaluated whether acyclovir treatment ($n = 106$) could have a beneficial effect on mortality as compared with the standard treatment ($n = 106$).
Results: Acyclovir treatment was positively linked to in-hospital and ICU-mortality reduction. This favourable influence remained present after correcting for possible confounders and using propensity-adjusted and propensity-matched cohorts: with an odds ratio in the treated group of 3.19 (95% CI 1.79–5.69, $p = 0.001$) for ICU survival and of 3.55 (95% CI 2.16–5.85, $p < 0.001$) for in-hospital survival. The subgroup with HSV-1 detected in the BAL-fluid is the sole contributor to this difference. In the BAL-fluid detected group, 48% ($n = 10$) of non-treated patients died in the ICU, versus 21% ($n = 6$) in the acyclovir-treated group ($p = 0.033$), occurring despite an even longer duration of ventilation or ICU stay.
Conclusions: These data highlight the hypothesis that it might be worthwhile to consider treatment of HSV-1 in ICU patients depending on the type of respiratory sample in which the virus is detected. These results warrant a prospective trial to prove causality.

1. Background

After primary infection herpes simplex virus type 1 (HSV-1) invades neurons and subsequently remains in a non-replicating form in the dorsal root ganglia and the autonomic nervous system [1]. During this latency period, viral reactivation can be caused by a wide range of stimuli [2–4]. The majority of HSV-1 infections in immunocompetent adults follow a benign course [1,5]. Occasional serious manifestations include infections of the central nervous system, mucocutaneous surfaces and visceral organs [1,5].

HSV-1 pneumonia has particularly been described in immunosuppressed patients [6,7]. On the other hand, HSV-1 is detected in a high percentage (22–32%) of the respiratory samples of intensive care (ICU) patients with an unknown clinical relevance [8,9]. Although this HSV-1 detection in the ICU is associated in some studies with increased morbidity and mortality, it is not known whether HSV-1 is an innocent bystander or harmful participant in critical illness.

2. Objectives

It may be that HSV-1 is reactivated in proportion to the severity of the underlying illness, with a genuinely attributable mortality [8,10–13]. So it remains unclear whether the use of an antiviral agent, i.e., acyclovir, could have a beneficial effect for critically ill patients in whom HSV-1 is detected. Therefore, we retrospectively analysed over an 8-year period all ICU patients with a positive

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BAL, bronchoalveolar lavage; BASP, bronchial aspirate sample; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; ETA, endotracheal aspirate; HSV-1, herpes simplex virus, type-1; ICU, intensive care unit; NFA, nasopharyngeal aspirate; OPS, oropharyngeal swab; SAPS-3, Simplified Acute Physiology Score-3; SOFA-score, Sequential Organ Failure Assessment-score.

* Corresponding author at: Department of Critical Care Medicine, Antwerp University Hospital (UZA), Wilrijkstraat 10, 2650 Edegem, Belgium. Tel.: +32 3 8213639; fax: +32 3 8284882.
E-mail address: Philippe.Jorens@uza.be (P.G. Jorens).
[1] Both authors contributed equally to this paper.
[2] Current address: ZNA, Antwerp, Belgium.

http://dx.doi.org/10.1016/j.jcv.2014.04.010
1386-6532/

HSV-1 culture in the respiratory tract and compared patients who had received acyclovir or had undergone standard treatment.

3. Study design

3.1. Study population

All adult patients (≥18 years) admitted for 10 days or longer to the Intensive Care Unit (ICU) of the Antwerp University Hospital (tertiary hospital of the University of Antwerp) between January 2004 and March 2012 and in whom HSV-1 was isolated from at least one respiratory sample (i.e., nasopharyngeal (NFA), endotracheal (ETA) or bronchial aspirate (BASP), sputum, bronchoalveolar lavage (BAL)), were eligible. Treatment for suspected respiratory tract infection with HSV-1 was not protocolised and both the initiation and termination of the treatment with acyclovir was left to the discretion of the treating physician. However, when administered during the whole period, it was always given intravenously at a dosage of 10 mg/kg t.i.d. over the course of 5–14 days unless renal function required a dose adaptation. Patients receiving acyclovir for prophylaxis (e.g., after bone marrow transplant) or antiviral agents for other reasons (e.g., HSV-1 encephalitis or gancyclovir for CMV infection) were excluded.

All HSV-1 positive cultures were retrieved from the hospital microbiological database. Although the study was not protocolised, the study protocol did not change throughout the study period. Respiratory samples were always taken as soon as respiratory symptoms or signs occur (worsening of respiratory condition after 48 h of ICU care with or without mechanical ventilation together with an infiltration in lungs; severe deterioration of ventilator settings (PEEP, rapidly worsening hypoxaemia), more mucus...). Therapy for HSV-1, if performed, was initiated as soon as the first sample was reported positive for HSV-1 (a mean of three days after taking the sample). Neither the management of our ICU patients, nor the dosage and duration of acyclovir, nor the way cultures were taken or executed changed.

The files of 317 ICU patients with a positive HSV-1 culture were considered for further analysis. 105 HSV-1 patients were excluded because the inclusion criteria were not fulfilled (see above), the medical records could not be completely retrieved or the records indicated a positive non-respiratory sample (skin lesions, $n = 10$).

3.2. Patient data

The records as well as the ICU Patient Data Management System (iMD-Soft MetaVision, available since June 2007) were searched for many general patient characteristics. The patient's history was reviewed for known risk factors for HSV-1 reactivation, such as diabetes, chronic heart failure and the chronic use of immunosuppressive drugs or steroids [7,14–17]. As markers of disease severity, the SAPS-3 (Simplified Acute Physiology Score) [18] and the SOFA (Sequential Organ Failure Assessment) score were taken into account as parameters for disease severity [19].

We considered the following data as relevant: total duration of ventilation and ICU stay, duration of ventilation after HSV diagnosis, ICU and in-hospital mortality, the administration of vasopressors and inotropic drugs and the use of corticosteroids during the ICU period. Patients who were not ventilated were not taken into account for the calculation of the ventilation duration time.

ARDS (Acute Respiratory Distress Syndrome) was defined based on the standard definition used at that time [20]: a PaO_2/FiO_2 score below 200 mm Hg and a standard X-ray with bilateral alveolar infiltrates not attributable to left heart failure.

3.3. HSV-1 detection

The samples were obtained from an airway (endotracheal and bronchial aspirate) or from bronchoalveolar lavage (BAL) fluid. Prior to this study period, oropharyngeal swabs (OPS) had been taken routinely [8]. In this study period, a culture for HSV-1 was only systematically performed for each airway and alveolar sample obtained during bronchoalveolar lavage (BAL). BAL is routinely performed if the haemodynamic and respiratory conditions allow it for every ventilated patient and in non-ventilated patients with a new infiltrate more than 48 h after admission. HSV-1 detection in other upper airway samples without BAL was only executed when specifically requested by the treating physician. In our centre, HSV-1 detection in respiratory samples is performed by validated viral culture [21,22].

Swabs (synthetic tipped on aluminium applicator; Copan-Medisch Labo Service, Menen, Belgium) were transported to the laboratory in 1 mL of virus transport medium (Dulbecco's minimal essential medium with 2% newborn calf serum and 50 μg/mL gentamicin). The sample was vortexed and centrifuged at 3000 rotations per minute for 30 min. 0.2 mL of supernatant was inoculated on VERO-cells (Bio-Whittaker, Verviers, Belgium) and incubated at 37 °C in a 10% CO_2 atmosphere. The cells were inspected every day for the typical cytopathogenic effect of HSV-1 growth: identification of HSV-1 was confirmed after subculture on shell vials and staining with specific monoclonal antibodies. Bronchus aspirate or BAL samples were transported to the laboratory in sterile containers with 3 mL of this virus transport medium and vortexed with glass beads. Subsequently, the procedure described above was used to complete the culture for HSV-1.

BAL samples were also cultured for bacteria and other respiratory viruses (cytomegalovirus, rhinovirus, adenovirus) as well as parainfluenza virus, influenza virus and respiratory syncytial virus, only from October to April.

3.4. Ethics

This study was conducted in accordance with the amended Declaration of Helsinki. The Ethics Committee of the Antwerp University Hospital waived the necessity for informed consent, as all data were gathered retrospectively and anonymously (EC approval 11/2/19).

3.5. Statistical analysis

Statistical analysis of the data was performed using the SPSS software, version 20.0.0 (SPSS, Inc., Chicago, IL, USA). Differences between the treated and untreated groups were assessed using the χ^2 test for the comparison of normally distributed categorical variables, and the independent samples t-test for continuous variables. The Kolmogorov–Smirnov test was used to test whether the continuous data were normally distributed. If the variable was not normally distributed, the Mann–Whitney U test was performed, and the data were represented as mean with range. A univariate and multivariate COX regression was performed for the treatment groups and for the individual other risk factors. Risk factors that were significantly associated with mortality in the univariate regression were included in a forward conditional multiple COX regression model. To control for potential confounding in this retrospective analysis, we used a propensity score matched cohort design. The propensity score is defined as the probability of acyclovir treatment, conditional on predefined factors. We polled the physicians of our department to define the factors which play a role in the decision whether a patient that tested positive for HSV-1 will receive acyclovir or not: renal impairment, generally sicker patient, immunosuppressive therapy, and a longer