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Pneumococcal polysaccharide vaccination administered early after neurotrauma or neurosurgery

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ABSTRACT

Objectives: Pneumococcal vaccination is recommended to lower the risk of posttraumatic meningitis, and early vaccination may be of importance. After both trauma and central nervous system injury, immunesuppression may occur, which could affect T-cell function and the response to T-cell dependent vaccines. We therefore aimed to investigate the response to early vaccination with a T-cell independent pneumococcal polysaccharide vaccine (PPSV).

Methods: Thirty-three patients with basilar skull fracture and 23 patients undergoing transsphenoidal pituitary gland surgery were vaccinated with PPSV within 10 days after neurotrauma or neurosurgery. Twenty-nine neurosurgical patients vaccinated ⩾3 weeks after neurotrauma or neurosurgery served as controls. Serotype-specific anti-polysaccharide binding IgG antibody levels to serotypes 4, 6B, 9V, 14, 18C, 19F and 23F were determined by enzyme immunoassay.

Results: The vaccination was safe and a highly significant antibody response was found against all serotypes in all groups ($p < 0.001$ for each of the serotypes). There were no differences between groups or in the group by time interaction in any of the serotypes. After early and late vaccination, protective levels were found in >80% for serotypes 9V, 14, 18C, 19F and 23F and in 70% and 50% for serotypes 6B and 4, respectively.

Conclusion: Patients vaccinated with PPSV within 10 days after neurotrauma or neurosurgery respond similarly to those vaccinated after ⩾3 weeks, indicating that PPSV can be administered early after neurotrauma or neurosurgery.

Conclusion: Clinical Trials registration: NCT02806284.

1. Introduction

Acute bacterial meningitis is a well-known and serious complication to neurotrauma, especially after basilar skull fracture. It is thought that basilar skull fractures expose the central nervous system to contamination by bacteria from the nose and throat, thereby increasing the risk of meningitis [1]. Injury to the anterior fossa including the paranasal sinuses may produce cerebrospinal fluid (CSF) leak with rhinoliquorrhoea. Trauma to the middle and the posterior skull base can affect the petrous bone and the mastoid air cells which may cause CSF leak with otorrhoea [2]. The over-all incidence rate of meningitis after neurotrauma is 10–15%. If persistent CSF leak is present, the rate is even higher [1,3,4]. Efforts to lower the risk include prophylactic antibiotics, although there is little evidence to support this regimen [1]. Vaccination against the most common causal agent in posttraumatic meningitis, *Streptococcus pneumoniae*, is an alternative approach [5,6]. Despite the lack of clinical trials, vaccination is recommended in several national guidelines [7–9]. In the USA, the Advisory Committee on Immunization Practices (ACIP) recommends that adults aged ⩾19 years with CSF leak should receive pneumococcal vaccination. In Sweden, the Public Health Agency until 2016 recommended that pneumococcal vaccination should be offered to all

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patients with basilar skull fracture regardless of visible CSF leak. In Swedish guidelines published in 2016, vaccination is now recommended only to patients with CSF leak. In none of the guidelines were there recommendations about when the vaccine should be given. Current clinical practice in Sweden is to vaccinate after the acute period has passed, leaving the patient without protection for several weeks. Because the risk for meningitis is at its highest within the first weeks after the trauma [3,10], it would be an advantage to vaccinate earlier, preferably only days after the trauma as the onset of the protection afforded by the vaccine is expected at earliest 2 weeks after vaccination [11].

However, trauma and surgery activate the innate immune system and induce a systemic inflammatory response syndrome in which pro-inflammatory and anti-inflammatory responses occur early and simultaneously [12]. A phase of net pro-inflammation is followed by net immuno-suppression with decreased T-cell function [13–16]. In order to prevent post-injury autoimmune aggression, patients with injuries of the central nervous system (CNS) may, in addition, show signs of a specific CNS injury-induced immune deficiency syndrome (CIDS), a condition also characterized by impaired T-cell activity [17]. Accordingly, it can be speculated that ongoing trauma-induced immune deficiency syndrome (TIDS) and CIDS by impaired T-cell function could negatively affect the response to vaccines, especially to T-cell dependent conjugate vaccines. An impaired response to this type of vaccine is somewhat supported by a recent study in which the number of responders was decreased and antibody concentration lower in patients with possibly ongoing TIDS and CIDS that were vaccinated with a T-cell dependent vaccine early after either neurotrauma or neurosurgery [18]. Because the humoral immune response has been reported to be less affected by CIDS [17], the response to a T-cell independent vaccine such as the pneumococcal polysaccharide vaccine (PPSV) might theoretically be less affected and if so, a better choice for an early vaccination resulting in protection shortly after the trauma when the risk of meningitis is at its highest [3].

The aim of the present study was therefore to investigate the response to a PPSV in patients vaccinated within 10 days from the onset of possible TIDS and CIDS after neurotrauma or neurosurgery and to compare the response with that in patients vaccinated after the acute period according to our standard regime.

2. Material and methods

2.1. Patients

Neurosurgical patients in the previously reported study on *Haemophilus influenzae* type b vaccination [18] were also vaccinated with a 23-valent PPSV (PPSV23). These patients were admitted to the Department of Neurosurgery, Uppsala University Hospital from 2001 to 2008 and prospectively included in the study in three different groups, neurotrauma (NT), neurosurgery (NS) and control groups. The NT group consisted of patients with basilar skull fracture with or without known CSF leak. Recruitment to the NS group was made from patients scheduled for elective, transsphenoidal pituitary gland surgery, constituting an intermediate group with a more limited neurotraumatic inflammatory insult compared with the NT patients. Patients who had undergone neurotrauma with or without basilar skull fracture or neurosurgery at least 3 weeks earlier were enrolled in the control group. Because traumatic brain injury, irrespectively of skull fractures, has been held as an important factor for CIDS and impaired T-cell response [17,19,20] patients with neurotrauma without skull fracture were also allowed in the control group. Control patients were referred from the Department of Neurosurgery to the Department of Neurological Rehabilitation, Uppsala University Hospital or to a local hospital in the patient's home county.

The study protocol was approved by the Regional Ethical Review Board at Uppsala University, Sweden (reference number 00-254). Consecutive patients were screened and included when vaccination and follow-up were possible to perform and informed consent had been obtained. The patients or their next of kin were asked about previous vaccinations against pneumococci.

2.2. Vaccination

All patients received a single subcutaneous injection of 0.5 ml Pneumovax® (Sanofi Pasteur MSD AB, Lyon, France) (PPSV23) in the left upper arm. A 0,5 ml dose of this vaccine contains 25 μg of purified capsular polysaccharide from each of the 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). Patients in the NT and NS groups were vaccinated within 10 days after trauma or surgery and control patients according to the local routine after an elapsed period of at least three weeks post-trauma or post-surgery. Adverse reactions to the vaccine were recorded.

2.3. Sera collection and analysis

Pre-vaccination sera were collected just before vaccination and post-vaccination sera were obtained 3 and 6 weeks after vaccination. Samples were stored at -70 °C pending analysis.

Serotype-specific anti-polysaccharide binding IgG antibody levels to serotypes 4, 6B, 9V, 14, 18C, 19F and 23F were determined by enzyme immunoassay which is an established and accredited methodology [21]. The laboratory was blinded with respect to group assignment of the patients.

The true correlate of protection for adults after vaccination with PPSV23 is not known [22]. A serotype-specific IgG >0.35 μg/ml has been defined as the correlate of protection for invasive disease in infant recipients of pneumococcal conjugate vaccine (PCV) [23]. The value of 1.0 μg/ml has been chosen as the target level of protection in other studies [24] and was therefore used as cut-off in the present investigation.

2.4. Calculation and statistics

In the analyses, the antibody levels of the NT and the NS groups were to be compared with those in the control group. Antibody levels were logarithmically transformed and expressed as geometric mean antibody concentrations (GMCs).

Linear mixed models were employed to analyze differences in antibody levels. The Chi-square test, using Akaikes IC and the degree of freedom from the fitted models, was performed to determine the best covariance structure. The covariance structure that best fitted the models was the unstructured one. The maximum likelihood method was applied to estimate the parameters for study group and time point for collected sera which both were treated as fixed effects in the models. Differences in proportion of patients with antibody levels $\geqslant 1.0$ μg /ml before and after vaccination were analyzed by Wilcoxon matched-pairs signed-rank test and differences in the number of responders by Fisher's exact two-tailed test. To analyze the relationship between post-vaccination concentrations and age and time from trauma/surgery, Pearson's product-moment correlation was computed.

The software GraphPad Prism (GraphPad Software, San Diego, CA, USA) and SPSS version 22 (IBM Corp., Amonk, NY, USA, 2015) were used for the statistical calculations. A p-value of <0.05 was considered significant. Values are given as mean ± SE, unless otherwise indicated.

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