Effect of Treatment on Maxillary Sinus and Nasal Nitric Oxide Concentrations in Patients With Nosocomial Maxillary Sinusitis*

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Study objectives: **In maxillary nosocomial sinusitis (MNS) related to severe sepsis, nitric oxide (NO) concentration in the maxillary sinuses is drastically reduced secondarily to a downregulation of type-2 NO synthase. NO plays a major role in nonspecific immune defense of sinuses. We therefore aimed to study maxillary NO concentration during the treatment of MNS with drainage, daily lavage, and removal of any nasally introduced tube.**

Patients and methods: **Nine patients were studied during the first 4 days of treatment of MNS. We measured the concentration of NO gas in the maxillary sinus and in the nasal cavity, and the NO metabolite levels (nitrites/nitrates [NOx]) in the sinus lavages.**

Measurements and results: **Maxillary NO concentration (median [25 to 75 percentile]) increased from 70 parts per billion (ppb) [40 to 100 ppb] to 2,050 ppb (1,700 to 3,000 ppb) after 4 days of treatment of MNS ($p < 0.0001$). In the meantime, nasal NO increased from a median of 100 ppb (98 to 148 ppb) to 180 ppb (180 to 188 ppb) [$p < 0.001$]. At any time, there was a correlation between maxillary NO (logarithmic value) and nasal NO ($r^2 = 0.57$, $p < 0.0001$). NOx levels remained stable in the lavages.**

Conclusions: **We conclude that the treatment of the sinusitis with drainage, daily lavage, and removal of the gastric tube lead to a spectacular increase of maxillary and nasal NO concentrations.** ***(CHEST 2005; 128:1699–1705)***

Key words: nitric oxide; nosocomial maxillary sinusitis; sepsis

Abbreviations: CRP = C-reactive protein; MNS = maxillary nosocomial sinusitis; NO = nitric oxide; NOS = nitric oxide synthase; NOS2 = type-2 nitric oxide synthase; NOx = nitrites/nitrates; PCD = primary ciliary dyskinesia; ppb = parts per billion; SOFA = sepsis-related organ failure assessment

Nitric oxide (NO) is implicated in a wide range of disease processes, exerting both detrimental and beneficial effects.[1] NO is a free-radical gas generated from L-arginine by a family of enzymes, the NO synthases (NOS).[2] NO generated by the type 2 NOS (NOS2) has a major role in nonspecific host defense in humans.[3] In most organs, basal expression of NOS2 and thereby basal NO concentrations are very low, while in case of inflammation or infection, NOS2 expression is induced and NO acts as a second line of defense.[4] In case of severe sepsis, induction of NOS2 results in sustained production of NO for a prolonged period of time, and this increased NO production plays a pivotal role in hypotension, leading to septic shock.[5] The scenario for host defense in the paranasal sinuses appears to be exactly the reverse: the epithelium constitutively expresses NOS2, leading to NO concentrations of 5,000 to 20,000 parts per billion (ppb),[6] whereas in case of maxillary sinusitis related to severe sepsis and septic shock, paranasal NO production is almost completely suppressed due to a downregulation of NOS2.[7]

Maxillary nosocomial sinusitis (MNS) is a frequently unrecognized cause of fever in critically ill

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patients.[8] Treatment classically consists in sinus drainage and lavages, nasal tracheal tube removal or tracheotomy, nasal gastric tube removal, and parenteral antibiotics.[9] The underlying mechanisms for fluid retention and compromised immune defense in MNS are poorly understood. The sinuses communicate with the nasal cavity through a narrow ostium. Blockage of this ostium by nasal tubing has been considered to be a central event in the pathogenesis of sinusitis, but this is still controversial.[10] Deja et al[7] have described a drastic reduction of maxillary NO concentration in patients with MNS. Simple inflammation of the sinus mucosa (without evidence of infection) was associated with dramatic inhibition of the expression of NOS2 within the epithelium. The resultant substantial decrease of intracavitary NO may account for marked impairments of nonspecific host defenses, thus promoting mucus accumulation and rapid superinfection.[11]

The aim of the present study was to investigate the effect of treatment of MNS (drainage, daily lavage, and removal of nasally introduced tubes) on NO concentration in the maxillary sinus and in the nasal cavity. We also measured NO metabolite levels (nitrites/nitrates [NOx]) in the sinus lavages.

Materials and Methods

Study Population

This prospective study was conducted in a 16-bed ICU at the teaching hospital in Toulouse, France. The study protocol was approved by the local ethics committee. Patients enrolled in the study fulfilled all the following criteria: (1) age > 18 years, (2) endotracheal intubation, (3) mechanical ventilation for > 72 h, and (4) criteria of severe sepsis, according to the current definition.[12] The worst simplified acute physiology score II during the first 24 h of intensive care stay was recorded.[13] The sepsis-related organ failure assessment (SOFA) score[14] was calculated retrospectively for the 4-day follow-up. For each patient, the worst value for each organ system (respiratory, cardiovascular, renal, coagulation, liver, and neurologic) in each 24-h period was considered. Patients were excluded from the study if they met at least one of the following criteria: (1) history of sinusitis, (2) transfer to the radiology department considered by the attending physician as a high risk of morbidity because of severe respiratory state, or (3) coagulation disorders contraindicating transnasal puncture. Patients underwent a routine fever workup that included a chest radiograph, urine analysis with culture, and blood cultures. When these studies failed to identify the source of the fever or if fever was persistent despite administration of antibiotics effective against isolated causative organisms of a diagnosed infection, CT of the paranasal sinuses (5-mm incremental thickness scans in the axial plane) was performed within 24 h. Maxillary sinusitis was defined as the presence of unilateral or bilateral opacification on a CT scan, reflecting air/fluid levels and/or opacification within the maxillary sinuses. Patients with radiographic maxillary sinusitis underwent transnasal puncture of the maxillary sinus involved and placement of an Albertini drain (Porges SAS; Le Plessis Robinson, France). The antibiotic regimen was not modified during the follow-up.

Microbiological Examination

Transnasal sinus puncture was performed by an otorhinolaryngologist using a standardized protocol; nostrils were disinfected with antiseptic solution (povidone-iodine solution). If necessary, a general anesthesia was induced, using a combination of sufentanyl and midazolam. Transnasal puncture of the maxillary sinuses was performed using an Albertini trocar. Sinus contents were directly aspirated prior to lavage and immediately transported for bacteriologic examination. An Albertini drain was left in the sinus cavity.

Gas Sampling and NO Measurements

For gas sampling in the sinus, the Albertini drain was connected to a glass syringe. The atmospheric NO in the room was controlled to be inferior to 5 ppb. We collected 250 mL of gas in aliquots of 50 mL with a continuous aspiration rate of 0.1 L/min. The five syringes were pooled in an inert plastic bag (Tedlar bag; Hoffmann-Plastiques; Saint-Etienne, France), and NO concentration was measured immediately by a chemiluminescence NO analyzer (Cosma; Igny, France) sampling with a constant flow of 0.7 L/min.

To measure nasal NO, we used the same chemiluminescence NO analyzer (Cosma) sampling with a constant flow of 0.7 L/min. The probe was connected to a nasal olive and gently introduced into the vestibulum of one nostril. The contralateral nostril was left open. Measurements were performed in both nostrils.

Lavages

The sinuses were irrigated with 20 mL of sterile saline solution in order to remove pus from the surface of the sinuses so that a "true" lavage could be obtained with minimal effects from bacterial debris.[15] Lavage was then performed with 5 mL saline solution and immediately reaspirated into a plastic syringe through the Albertini drain. The lavage was immediately placed on ice, removed from light, and subsequently stored at $-80°C$ until assay for NOx was performed.

Measurement of NOx

Samples were assayed in duplicate for oxidation end-product of NO (NOx). Nitrate (NO_3^-) in the samples was first reduced to nitrite (NO_2^-) by incubating the samples for 1 h with *Escherichia coli* nitrate reductase enzyme prepared from bacteria grown under anaerobic conditions, in the presence of nicotinamide adenine dinucleotide phosphate and flavine adenine dinucleotide (Boehringer-Mannheim; Mannheim, Germany). NO_2^- levels were then determined by the Griess reaction by measuring the absorbance of each sample at 543 nm. The total amount of nitrite was expressed in micromoles per liter.

Statistics

The data were expressed as median (25 to 75 percentiles). Comparisons were made by the Friedman analysis of variance followed by posttests of Wilcoxon with a correction of Bonferroni. The correlation analysis was performed with the Pearson correlation test for $n > 30$ and with the Spearman correlation test for $n < 30$; $p < 0.05$ was considered significant. Analysis was performed using statistical software (SPSS version 11.0; SPSS; Chicago, IL).

Results

A total of nine patients fulfilling the inclusion criteria completed the whole procedure during a