Dexamethasone for Parapneumonic Pleural Effusion: A Randomized, Double-Blind, Clinical Trial

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Objective To assess whether dexamethasone (DXM) decreases the time to recovery in patients with parapneumonic pleural effusion.

Study design This was a multicenter, randomized, double blind, parallel-group, placebo-controlled clinical trial of 60 children, ranging in age from 1 month to 14 years, with community-acquired pneumonia (CAP) and pleural effusion. Patients received either intravenous DXM (0.25 mg/kg/dose) or placebo every 6 hours over a period of 48 hours, along with antibiotics. The primary endpoint was the time to recovery in hours, defined objectively. We also evaluated complications and adverse events.

Results Among the 60 randomized patients (mean age, 4.7 years; 58% female), 57 (95%) completed the study. Compared with placebo recipients, the patients receiving DXM had a shorter time to recovery, after adjustment by severity group and stratification by center (hazard ratio, 1.95; 95% CI, 1.10-3.45; $P = .021$). The median time to recovery for patients receiving DXM was 68 hours (2.8 days) shorter than patients receiving placebo (109 hours vs 177 hours; $P = .037$). In exploratory subgroup analysis, the median time to recovery for patients with simple effusion receiving DXM was 76 hours (3.1 days) shorter than for patients with simple effusion receiving placebo ($P = .017$). The median time to recovery for patients with complicated effusion receiving DXM was 14 hours (0.5 days) shorter than for patients with complicated effusion receiving placebo ($P = .66$). The difference in the effect of DXM in the 2 severity groups was not statistically significant ($P = .138$ for interaction). There were no significant differences in complications or adverse events attributable to the study drugs, except for hyperglycemia.

Conclusion In this trial, DXM seemed to be a safe and effective adjunctive therapy for parapneumonic pleural effusion. *(J Pediatr 2017;185:117-23).*

Trial registration ClinicalTrials.gov: NCT01261546.

Parapneumonic effusion complicates 2%-13% of cases of hospitalized pneumonia, leading to long hospitalizations.[1-5] To our knowledge, corticosteroids have not been the subject of trials for parapneumonic effusion. Corticosteroids block inflammatory cytokine genes that are key factors in the first, exudative stage of pleural effusion.[6-8] Although this is controversial, some trials have suggested that dexamethasone (DXM) may be useful in meningitis, septic arthritis, and adults with community-acquired pneumonia (CAP).[9-13]

We hypothesized that the concomitant treatment of antimicrobials and early administration of DXM would prove beneficial in parapneumonic pleural effusion. Positive results would be seen in the early phases, before an excessive inflammatory response developed. Our aim in this study was to investigate whether the concomitant treatment of DXM (0.25 mg/kg/dose every 6 hours for 48 hours) with antibiotic therapy decreased the time to recovery of parapneumonic pleural effusion compared with placebo.

Methods

Corticoids for Pleural Effusion and Empyema (CORTEEC) was a multicenter, double-blind, parallel-group, placebo-controlled clinical trial (ClinicalTrials.gov:

CAP	Community-acquired pneumonia	PCV13	Pneumococcal conjugate vaccine
CRP	C-reactive protein	SaO_2	Oxygen saturation
DXM	Dexamethasone	VATS	Video-assisted thoracic surgery

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Funded by the Spanish Ministry of Health (EC10-014) and the Sociedad de Pediatría de Madrid y Castilla La Mancha (2011). Kern Pharma, Inc, Barcelona, Spain, supplied the drugs (dexamethasone and saline) and randomization. They had no role in the study design, data collection and analysis, or drafting of the manuscript. The authors declare no conflicts of interest.

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NCT01261546). The aim of this trial was to provide information on the safety and potential for effectiveness of DXM over placebo. The study was conducted in Spain at 9 urban university-affiliated public hospitals over a period of 55 months. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. The study was approved by the Institutional Review Board of each of the 9 hospitals.

Eligible participants were hospitalized children aged 1 month to 14 years with CAP and pleural effusion. CAP was defined as fever >38 °C, cough, and parenchymal infiltrate on chest radiography. All patients underwent chest radiography and thoracic ultrasound. Written informed consent was obtained from a parent of each child. Exclusion criteria were proven allergies to any study drugs or treatment with corticosteroids, immunodeficiency, any concomitant disease likely to worsen with corticosteroid treatment and any condition that prevented participation in the study.

Randomization and Masking

Randomization was stratified by center and severity of disease (ie, complicated or simple effusion). Eight centers had planned to recruit 7 patients each. Patients were classified as having complicated effusion or simple effusion. Complicated effusion was defined as pH <7.2 or loculations or septations on ultrasound, or bacteria on Gram stain. Simple effusion was defined as effusion not fulfilling any of those criteria (**Table I**; available at www.jpeds.com). Patients of each center were assigned in a 1:1 ratio to each treatment group using a computer-generated randomization scheme performed the manufacturer of the study drug (Kern Pharma, Barcelona, Spain).

The participants, care providers, data manager, and investigators were all blinded until the end of the study. Kern Pharma provided prepackaged boxes for each patient containing either 15 transparent ampules of the study drug, 4 mg/mL DXM phosphate (in 1-mL ampules), or 15 ampules of the placebo, 0.9% NaCl (in 1-mL ampules). The placebo was identical in appearance, color, size, and packaging to DXM. Care providers and researchers were blinded to the content of the ampules. The boxes were numbered consecutively for each hospital, severity stratum, and patient, according to the randomization scheme.

Twenty-eight months into the study, with 36 patients recruited, 2 unexpected severe adverse events occurred (1 death and 1 need for insulin). After receipt of permission from the Institutional Review Boards and the Spanish Drug Agency, a masked interim analysis was performed to test the safety and futility of the trial. The Spanish Drug Agency reviewed and analyzed the results of the analysis. The trial was deemed safe and not futile, and so the trial continued. Competitive recruitment was allowed for up to 16 patients per center, and 1 new center joined (**Table II**; available at www.jpeds.com). No further changes in methods were made after the start of the trial.

Procedures

Patients were scheduled for 8 intravenous doses of DXM, 0.25 mg/kg every 6 hours or the corresponding volume of placebo over 48 hours. The first dose was administered within 12 hours after the diagnosis of pleural effusion. DXM or placebo was administered immediately after the first dose of cefotaxime, at a dose of 50 mg/kg/6 hours. Ranitidine (5 mg/kg/day intravenously in 2 doses over 48 hours) was administered concomitantly to prevent gastric bleeding. Cefotaxime was continued until 48 hours after the patient was afebrile, then switched to amoxicillin-clavulanate (80 mg/kg/day) to complete the 15-day antimicrobial therapy.

Patients with simple effusion received only medical treatment. Diagnostic thoracentesis was recommended if effusion was >10 mm on the ultrasound image. If biochemical data indicating complicated effusion were found, appropriate drainage was recommended. The recommended management for complicated effusion was medical treatment plus pleural drainage and fibrinolytics, or video-assisted thoracic surgery (VATS). Patients with an immediate need for thoracentesis, drainage, or VATS were included in the protocol. Nevertheless, a conservative approach without drainage was permitted at the discretion of the clinician, given that some studies have shown that pleural drainage is not always necessary. Blood tests (ie, hemoglobin, white blood cell count, and C-reactive protein [CRP]) were performed at the time of diagnosis. Ultrasound and blood tests were repeated at least 48 hours after recruitment, to analyze changes.

Outcomes

The primary outcome was time to recovery, measured in hours. Recovery criteria were continuous ambient oxygen saturation (SaO_2) >92%, continuous temperature <37°C, no respiratory distress, end of invasive procedures, pneumonia in resolution, and oral feeding. The presence of all criteria were necessary to classify a patient as recovered. Time to recovery was calculated from the first dose of trial treatment until the time when all recovery criteria were fulfilled; for fever, this was the first hour of absence of fever (**Table III**; available at www.jpeds.com).

The secondary outcomes measured were safety, such as complications of disease from the moment of hospitalization until day 30 after discharge (**Table IV**; available at www.jpeds.com), and adverse events attributable to corticosteroids during hospitalization (**Table V**). Other secondary endpoints included the progression of simple effusion to complicated effusion requiring chest drainage, decreased CRP level, and decreased effusion during days 1-3.

Statistical Analyses

A sample size of 56 patients (28 patients per group) were needed to detect a reduction in time to recovery of ≥24 hours (assuming an SD of 31 hours, 80% power, a 2-sided α level of 5%, and a 10% dropout rate). The SD was obtained from a small observational pilot study, where we observed an SD of 31 hours in time to recovery in children treated with steroids who had a pleural effusion.

We performed an intention-to-treat analysis. We assessed differences in time to recovery based on treatment group. We managed the missing outcome of the patient who died by