THE EFFECTIVENESS OF USING PREDNISOLONE IN CHILDREN WITH COMMUNITY–ACQUIRED PNEUMONIA

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Abstract: *community-acquired Pneumonia (CAP) is an infection of the lung parenchyma that is acquired outside of hospital,[1] involved approximately 150 million new cases annually, among children younger than 5 years old worldwide. We retrospectively evaluated the effect of Prednisolone in 89 children with CAP who were admitted to the 2nd hospital of Shandong University (China) and Infectious diseases of Andijon region (Uzbekistan). The mean age was 6.3 in China (Placebo) and 9.3 in Uzbekistan (control) years, 54% and 52% of them were boys respectively. All children had received broad spectrum antibiotics (cephalosporin) or Macrolides (Azithromycin) and Oxygen. In addition to these we added Prednisolone 1 mg/kg on day 2 of admission to control group. 24 (68.5% from all febrile) children were became afebrile within 24 hours after Predisolone use on day 3 of admission, and their clinical status developed in control group, when it was achieved on day 7 in Placebo group. Hospital days also shortened in control group (6 days) than placebo (8 days) (p value ≤ 0.01). In conclusion, steroid therapy helpful for reducing hospital stay and morbidity in children with community-acquired Pneumonia and no observed side effects.*

Keywords: *prednisolone, pediatric pneumonia, hospital day, placebo, corticosteroid, hospitalization, temperature, cough, morbidity.*

ЭФФЕКТИВНОСТЬ ПРЕДНИЗОЛОНА У ДЕТЕЙ С ВНЕБОЛЬНИЧНОЙ ПНЕВМОНИЕЙ

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Аннотация: *внебольничная пневмония - это инфекция легочной паренхимы, приобретенной вне медицинских учреждений. Во всем мире ежегодно встречается примерно 150 миллионов новых случаев у детей младше 5 лет. Мы ретроспективно исследовали 89 детей с внебольничной пневмонией, положенных во вторую больницу Шандонского университета (Китай) и Андижанскую областную инфекционную больницу. Средний возраст больных в группе плацебо (в Китае) был 6.3, в контрольной группе (в Андижане) равнялся 9.3 лет жизни. 54% процентов из 46 составили мальчики в группе плацебо, почти такое соотношение (52%) на контрольной группе. Все дети приняли антибиотики (цефалоспорины или азитромицин) и Кислород. Дополнительно к ним мы назначали Преднизолон (1*

мг/кг) детям, находящимся в Андижане, со второго дня на больничной койке. У 68.5% детей с повышенной температурой тела улучшилась их температура после принятия преднизолона уже через 24 часа и клинический статус тоже улучшился в контрольной группе. В плацебо группе мы пришли к этому результату на седьмой день госпитализации. Больничные дни тоже стали меньше в контрольной группе, чем в плацебо (6 дней к 8, p value ≤ 0.01). В заключение я хотел бы сказать: кортикостероидная терапия помогла уменьшить больничные дни, заболеваемость и смертность у детей с внебольничной пневмонией, без обнаружения ярко выраженных побочных эффектов.
Ключевые слова: *преднизолон, пневмония, плацебо, температура, кортикостероид.*

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Background: Community-acquired pneumonia afflicts all age groups and although not always bacterial in origin, is clinically versatile, depending on its cause. Pediatric pneumonia is also common, and first-line treatment is still amoxicillin, followed closely by cephalosporin or Macrolides. The definition of CAP varies between different sources; on a pathological level, pneumonia is considered infection of the lung parenchyma, i.e., lower respiratory tract (LRT) infection by microorganisms[2]. CAP is defined clinically as "the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital" by both the British Thoracic Society (BTS)[3]. CAP is an alveolar infection that develops in the outpatient setting or within 48h of admission to a hospital. Worldwide, pneumonia was responsible for 15% of childhood deaths in 2013, with highest incidence in developing countries[4]. The global annual incidence of pneumonia is 150 to 156 million cases, accounting for approximately 10-20 million hospitalizations. Physical signs of pneumonia are predominantly tachypnea, fever and crackles, rhonchi, or bronchial breath sounds, which can be heard on auscultation[5].The gold standard usually considered in the investigation of predictive signs of pneumonia is radiologically-confirmed pneumonia. Radiologic findings consistent with pneumonia include pulmonary infiltrate, either alveolar or interstitial[6]. Prolonged hospitalization could be associated with unfavorable outcomes and is also a cost burden to the public. Several preventable risk factors have been reported to be associated with prolonged hospitalization among children with severe community acquired pneumonia. Failing to exclusively breastfeed for the first 6 months, inappropriate complimentary feeding, anemia, malnutrition, exposure to parental smoking, inadequate antibiotic use, lack of awareness of parents, overuse of nonsteroidal anti-inflammatory drugs, and indoor air pollution contribute to prolonging duration of hospitalization. In my opinion, the accelerated recovery of wellbeing and reduction of hospital stay is of major added value. In European countries, the median estimated cost of median length of stay ranges from €1200 to €6900, with most of the expenses being related to hospital stay and staff [36]. Therefore, the corticosteroid-associated reduction in length of hospital stay should translate into substantial cost savings. Likewise, reduction in the use of antibiotics is potentially of major added value for the community.

METHODS:

Placebo-controlled, parallel group clinical trials.

Inclusion criteria: All patients with symptoms and signs indicative of pneumonia at admission, including fever (>38.4C per axilla), cough, and abnormal breath sounds on auscultation.

Exclusion criterias are permanent inability for informed consent, active intravenous drug use, acute burn injury, gastrointestinal bleeding within the past 3 months, known adrenal insufficiency, severe immunosuppression defined as one of the following: infection with human immunodeficiency virus and a CD4 cell count below 350 cells per μL, immunosuppressive therapy after solid organ transplantation, cystic fibrosis, or active tuberculosis.

We collected dependent variables like demographics (age, sex, and address) of the child; clinical presentation (cough, fever, difficulty breathing, grunting, cyanosis, convulsions, inability to feed, and change in level of consciousness), previous history of similar problem, immunodeficiency (HIV, malnutrition, and diabetes mellitus), physical examination (vital signs, nutritional status, intercostal or subcostal retraction, nasal flaring, chest in-drawing, wheezing, crepitations, bronchial breath sounds, cyanosis, signs of rickets, and mental status), and laboratory results (white blood cell count, absolute neutrophil count, hemoglobin, platelet count, C-reactive protein, erythrocyte sedimentation rate, and blood culture). The children are followed during their stay in the hospital for evaluation of oxygen requirement, antibiotics therapy, feeding, and persistency of fever, tachypnea, and duration of hospital stay and treatment outcome.

Eligible patients will be assigned (1:1 ratio) to receive either 1mg/kg of Prednisolone or placebo daily for 3-4 days. All children in an infectious diseases hospital of Andijan had received Prednisolone 1 mg/kg i/v, they are control group. Children admitted to the 2nd hospital of Shandong University considered as a placebo group. Statistical analyses were performed using SPSS software (version 23.0). Normal distribution data were expressed as mean ± SD (x±s). Independent-Samples T-test was used to compare these data. Statistical significance was defined as $P<0.05$

Results: We had 46 children in China, 2nd hospital of Shandong University who were not admitted Prednisolone – placebo group, and 43 children in an infectious diseases of Andijan region admitted Prednisolone

(1mg/kg intravenously) – control group. Placebo group patients' mean age was 6.3, (5 to 15 years old), 25 of them were boys.

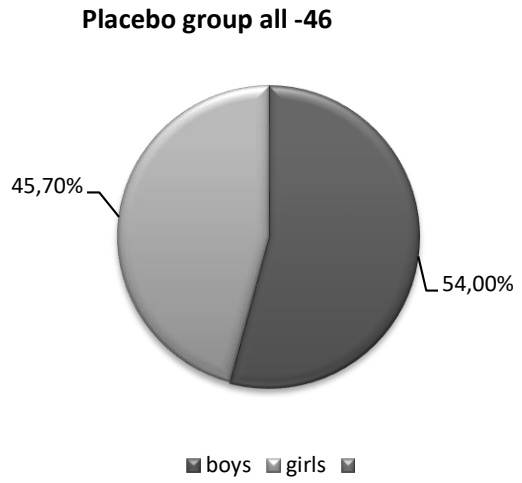

Fig. 1. Placebo group patients

All children had been radiologically confirmed with pneumonia. 21.7% of them were admitted CPAP (increased RR), and no complications. 8 of them were observed recurrences within 1 month with Pneumonia. Average hospital stay was 8 days, maximal is 22 days. 5 children had only increased temperature, 9 patients with cough, and 32 with both symptoms (cough + temperature).

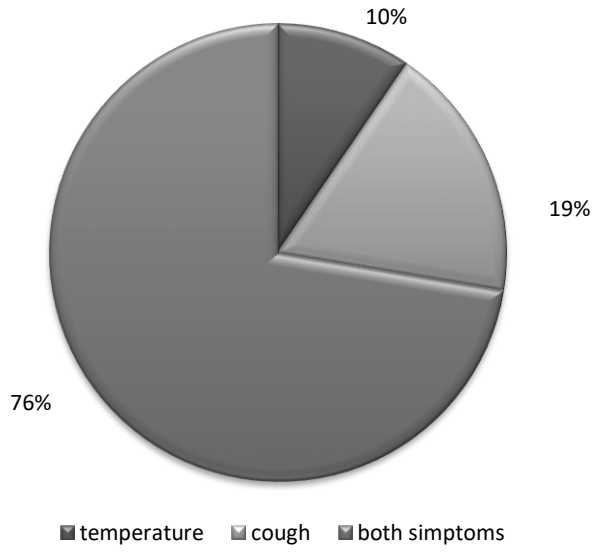

Fig. 2. Placebo group patients' symptoms on admission

13 patients had increased WBC.

The control group patients are 43, 22 of them were boys, the mean age was 9.3.

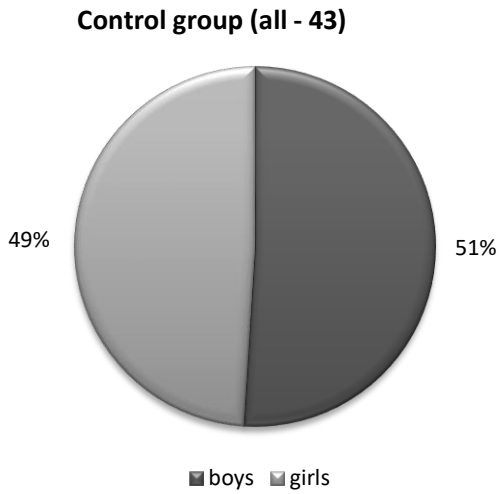

Fig. 3. Control group patients

All had radiologic confirmed Pneumonia, with increased RR. 8 children took CPAP, no recurrences. From the 2nd day of admission they took Prednisolone 1mg/kg intravenously, during the 4-5 days. 14 children had increased temperature on admission day, 9 with cough, 17 had both symptoms.

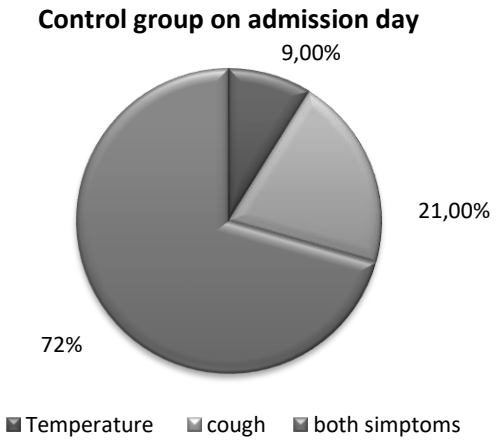

Fig. 4. The control group patients' symptoms on admission

Outcomes: 52.5% children with increased temperature (from 40) was afebrile on 4th day of admission, in placebo group. In contrast, 68.5% of patients from the control group achieved that on day 3.

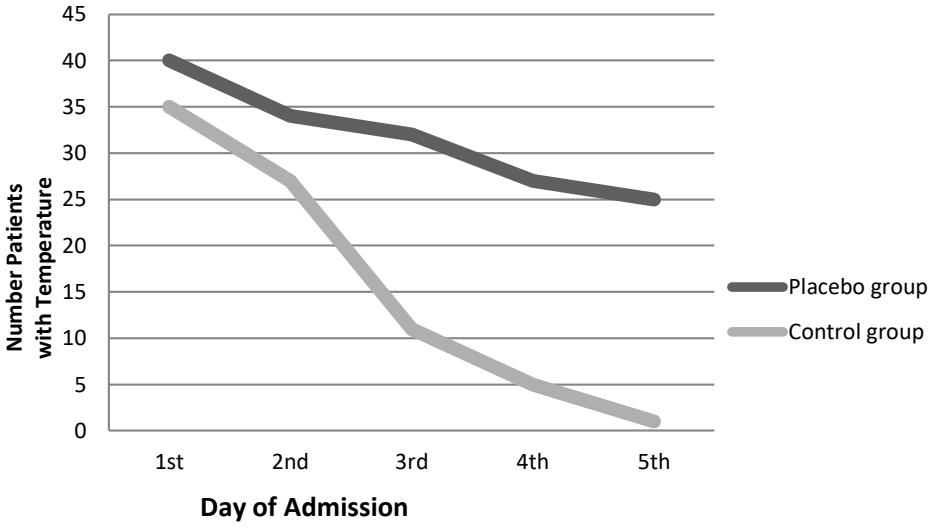

Fig. 5. The temperature line of two group patients

Placebo group children (56.8%) had been taken their cough at 7th day, when it was observed almost in all children (92.5%) in Control group**.**

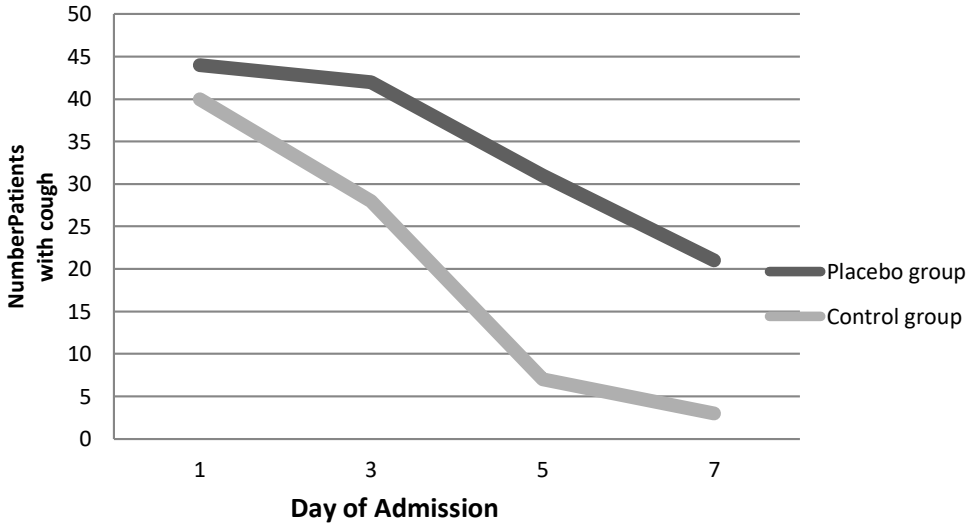

Fig. 6. The cough line of two group patients

Table 1. The mean difference of patiens

Variables	Placebo group	Control group	Mean Difference
Hospital days	8	5.93	2.07***
Temperature days	4.43	1.86	2.57***
Cough days	6.52	3.0	3.52***
Number of observations	46	44	

Note: Mean differences for selected variables between two group patients were estimated using independent samples T-test. ***, ** and * denote significance at 0.01, 0.05, and 0.10 levels, respectively.

Discussion part.

The favourable benefit-to-risk ratio noted with corticosteroids in this trial is in line with findings from trials done in Egypt[7], Italy[8], Japan[9], the Netherlands[10] and Spain[11] etc. Only one trial did not show benefit from corticosteroids[12]. Data from these trials accounting for 1379 adults with community-acquired pneumonia showed that adjunct treatment with corticosteroids reduced length of hospital stay (mean difference –1·10 days, 95% CI –1·86 to –0·34;)[13].

Among children with bacterial pneumonia, corticosteroids reduced early clinical failure rates (defined as for adults, RR 0.41, 95% CI 0.24 to 0.70; high-quality evidence) based on two small, clinically heterogeneous trials, and reduced time to clinical cure[14]. People with CAP treated with corticosteroids had lower clinical failure rates (death, worsening of imaging studies, or no clinical improvement), shorter time to cure, a shorter hospital stay, and fewer complications[14]. Claudine Angela Blum and colleagues5 report that 7-day treatment with 50 mg oral prednisone daily hastened recovery and hospital discharge in adults with community-acquired pneumonia of any severity[15].

A 2011 Cochrane review that included relevant CAP studies through the year 2010 showed that corticosteroid use accelerates time to symptom resolution and clinical stability, with infrequent adverse effects[16]. Similarly, a 2015 systematic review by Siemie-Niuk and colleagues included studies from 2011 through mid-2015[17]. Their analysis of 13 randomized controlled trials found significantly decreased mortality in severe pneumonia, decreased need for mechanical ventilation, decreased occurrence of acute respiratory distress syndrome, decreased time to clinical stability, and shorter duration of hospitalization[6].

A Spanish study was performed as a multicenter, randomized, double-blinded, parallel-group, placebo-controlled clinical trial. Sixty children, aged from 1 month to 14 years, with CAP and pleural effusion were included. Those authors described faster recovery rate, measured objectively in hours, in the group that received dexamethasone (DXM) 0.15 mg/kg, every 6 h, for 48 h, plus cefotaxime, when compared with the control group. There were no significant differences in adverse events attributable to the study drugs, except for hyperglycemia. Therefore, the authors concluded that DXM appeared to be a safe and effective adjunctive therapy for decreasing the time to recovery in children with parapneumonic pleural effusion[18]. Another study included children with severe CAP: 29 patients received a 5-day methylprednisolone course plus imipenem and 30 patients received imipenem plus placebo. The authors reported that the methylprednisolone group had a faster resolution of symptoms[19]. A recent systematic review identified four randomized controlled trials that included 310 children; corticosteroids reduced early clinical failure rates (RR 0.41 [95% CI: 0.24---0.70]; high-quality evidence based on two small, clinically heterogeneous trials, and reduced time to clinical cure[14]. To date, the role of corticosteroids in adjunctive chemical therapy of childhood CAP is yet to be established. Further support is needed to recommend the use of corticosteroids in clinical practice across distinct severity subgroups and in association with different antibiotics, especially þ-lactams[20].

Korean scientists concluded that corticosteroid treatment appeared to be temporally associated with clinical and radiographic improvement, and may be helpful for reducing morbidity in children with macrolide-nonresponsive severe MP.

From the rapid improvements of clinical symptoms and pulmonary lesions in the severe MP patients treated with corticosteroids, it has been proposed that cell-mediated immunity plays an important role in the progress of MP[21]. Studies of immune status in MP infection show a low incidence of MP in immunocompromised patients[22], and pulmonary lesions are usually minimal in immunodeficient children[23]. In animal studies, mycoplasma pulmonary lesions in cell-mediated immunity deficient animals induced by thymectomy, irradiation, or antithymus sera were significantly less severe than those in controls[24]. In other experimental Mycoplasma pneumoniae models, interleukin-2 was postulated to play a crucial role in the development of pulmonary lesions[25]. M. pulmonis-infected mice treated with minocycline and prednisolone had lower pulmonary lesion scores than mice treated with minocycline alone[26]. Abnormalities of cell-mediated immunity, including transient anergy to purified protein derivative (PPD), are described in adults as well as children after MP[27]. Pathological studies also provide evidence of cell-mediated immunity for MP pneumonia. When experimental animals are infected with mycoplasma, a large number of lymphocytes, mainly CD4 T-cells, initially infiltrate the peribronchiolar and perivascular regions, with phagocytes appearing later in the bronchiolar lumens [28], [29].

These observations suggest that cell-mediated immunity plays an important role in the development of progressive pulmonary lesions in severe MP. Corticosteroid therapy may render great benefit in helping to reduce morbidity in children with severe macrolide-non-responsive MP[30].

Rapid resolution of infection in 86 out of 90 children with complicated MPP who received systemic steroids[31]. Prednisolone appears to be the most effective corticosteroid in the adjunctive therapy of CAP, as it inhibits platelet activation in vitro by a non-genomic mechanism not shared with other types of corticosteroids[32]. Use of steroids could lead to earlier clinical and radiological resolution than antibiotics alone[33]. A recent large multicenter retrospective study in Japan identified 2,228 adult patients with MPP. The effects of low-dose and high-dose corticosteroid therapies on mortality, hospital length of stay (LOS), drug costs and hyperglycemia requiring insulin treatment of MPP were evaluated. However, adjunctive corticosteroid therapy did not decrease 30-day mortality. In addition, both low-dose and high-dose corticosteroid therapies were associated with increases in LOS. Furthermore, hyperglycemia requiring insulin treatment and drug costs increased with corticosteroid use[34]. Therefore, currently, the benefits of treating MPP patients with steroids needs further study. It has shown positive effects in children[35].

Conclusion.

Our small research has showed that corticosteroid therapy in children helped to reduce morbidity and hospital stay. Unanswered issues remain, on which researchers should focus their attention. First, evidence for a benefit from corticosteroids in outpatients with community-acquired pneumonia is still missing; second, the survival benefit of corticosteroids in patients with community-acquired pneumonia in the ICU still needs large confirmatory trials. Finally, researchers should also investigate any possible long-term benefit from corticosteroids owing to the growing evidence of long-term sequelae following severe infections.

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