Research Paper

Effect of Imipenem on Clinical Efficacy and Inflammatory Markers of Severe Pneumonia

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We attempt to discuss the improvement of clinical efficacy of imipenem in intensive care unit patients with severe pneumonia and its effect on serum C-reactive protein, procalcitonin and interleukin 6. We selected 70 patients with severe pneumonia who accepted therapy in intensive care unit of our hospital from February 2019 to June 2021 as participants. Randomly divided them into two groups, one was an experimental group and the other was control group (n=35). Treated control group with routine treatment such as anti-infection, phlegm and mechanical ventilation and other basic therapies, after receiving the same treatment as control group, treated experimental group with another imipenem, then compared both groups on acute physiology and chronic health evaluation II score, clinical effective rate, arterial blood gas and serum procalcitonin, C-reactive protein, interleukin 6 before and after therapy. After 3 d and 7 d treatment of groups, acute physiology and chronic health evaluation II score and partial pressure of carbon dioxide of experimental group had a greater downward trend than control group, but partial pressure of oxygen had a faster upward trend than control group. There was a remarkable difference, so it possessed statistical significance ($p<0.05$). Serum procalcitonin, C-reactive protein and interleukin 6 of experimental group had a greater downward trend than control group, with remarkable divergences ($p<0.05$). Total clinical effective rate of experimental group (91.4 %) was remarkably higher than control group (71.4 %) and it possessed significant difference ($p<0.05$). Imipenem can significantly improve the clinical effective rate of severe pneumonia, reduce the concentration of serum procalcitonin, C-reactive protein and interleukin 6, and provide clinical guidance value for the effective treatment of severe pneumonia.

Key words: Imipenem, severe pneumonia, clinical efficacy, C-reactive protein, procalcitonin, interleukin 6

Severe pneumonia is still a common type of critical illness in Intensive Care Unit (ICU) hospitalized patients, mainly related to *Streptococcus pneumoniae* infection[1]. Studies have reported that atypical pneumonia related to *Chlamydia pneumonia* and *Mycoplasma pneumonia* accounts for 1 %-30 % of ICU pneumonia hospitalized patients[2]. It has main clinical characteristics such as persistent fever, dyspnea, high fever and multiple organ dysfunction, etc. Some patients appear irritability, lethargy, coma and even death[3]. Most severe pneumonia patients in ICU need mechanical ventilation, while there are acute and critical cases, tracheotomy is required. The severity depends on respiratory function, systemic inflammatory response and *so on*[4].

Nuclear Factor kappa light chain enhancer of activated B cells (NF-κB) is an important transcription factor in severe pneumonia, which can regulate a variety of inflammatory responses. It can be activated by certain inflammatory factors, including Interleukin 1 beta (IL-1β), Tumor Necrosis Factor Alpha (TNF-α) and bacterial Lipopolysaccharide (LPS)[5]. When cells are irritated, NF-κB related signaling pathways are activated to release inflammatory factors in the body[6]. Many studies have proved that recently antibiotic treatment is the standard therapy for pneumonia caused by *Klebsiella pneumoniae*[7]. However, some *Klebsiella pneumoniae* strains have tolerance to antibiotics, including ciprofloxacin, carbapenem and colistin[8]. Since the currently used antibiotics are ineffective, we need to develop new therapies that are not resistant to *Klebsiella pneumonia*. However, we haven't cleared

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the current clinical efficacy of antibiotics in severe pneumonia treatment yet. This study observed the short-term and long-term efficacy of imipenem in severe pneumonia treatment and its effect on C-Reactive Protein (CRP), Procalcitonin (PCT) and Interleukin 6 (IL-6), in order to provide reference for finding a safe and effective method to improve the efficacy and prognosis of severe pneumonia[9]. Please check the following report.

MATERIALS AND METHODS

General information:

We selected 70 patients with severe pneumonia who accepted therapy in ICU of our hospital from February 2019 to June 2021 as participants.

Inclusion criteria: Meet the standards of "The US Guidelines for the Management of Hospital-acquired Pneumonia in 2005"[10] and "Expert consensus on clinical practice of emergency severe pneumonia in China", confirmed severe pneumonia patients clinically; patients without communication or mental disorders; patients without immune system diseases; patients and their families have signed informed consent.

Exclusion criteria: Patients with liver, kidney and other important organ diseases; patients with cardiovascular diseases; patients with unstable vital signs; have a history of cancer; complicated with severe obstructive pulmonary diseases. This study had got approval from the ethics committee of our hospital.

We randomly divided them into two groups, one was an experimental group and the other was control group (n=35). 18 males and 17 females included in control group, ages were from 41 y to 74 y old and average was about (62.8±8.04) y old. 16 males and 19 females included in experimental group, ages were from 39 y to 73 y old and average was about (62.22±8.64) y old. General information such as gender and age of both groups possessed no significant difference and can be compared as shown in Table 1.

Method:

After admission, both groups received regular therapies, including conventional resolving phlegm, relieving cough, volume expansion, maintaining homeostasis of internal environment, oxygen inhalation and mechanical ventilation when necessary, routine anti-infection, adopted anti-infective treatment such as cefotaxime sodium before drug sensitivity results coming out, made related adjustments according to drug sensitivity results during this period, nurses routinely carry out mechanical ventilation nursing, airway management, condition monitoring, nutritional support and *so on*, strictly monitor the vital signs and respiratory function of each patient to detect respiratory failure and other complications as early as possible[11]. Treated experimental group with imipenem based on these conventional therapies, imipenem and cystatin sodium for injection (MSD Pharma (Hangzhou) Pte. Ltd, NMPN: J20130123) 1.0 g intravenous drip every 12 h (q12 h), 1 w is a course of therapy.

Observation indicators:

Detection of CRP, PCT and IL-6 concentration levels in peripheral blood serum: Collected 5 ml fasting elbow vein blood from both groups in the early morning of the 2nd d after admission and placed them into two centrifuge tubes, 3 ml each. Placed one of the tubes for 30 min under room temperature condition, then centrifuged at a 3500 r/min centrifuge (4°) for 10 min, extracted supernatant and adopted enzyme-linked immunosorbent assay to exam CRP, PCT and IL-6 concentration levels in peripheral blood serum. After 3 d and 1 w treatment, repeated the same detection as above.

Clinical efficacy:

Adopted "Guiding Principles for Clinical Application of Antimicrobial Agents (2015 version)"[12] which was joint released by National Health and Family Planning Commission, People's Liberation Army General Logistics Department and Ministry of health and State Administration of Traditional Chinese Medicine in July 2015 as efficacy criteria, evaluated the clinical efficacy based on four indicators: Symptoms, signs, laboratory examinations and etiology; cure+markedly effective; the patient's condition has improved significantly and the four indicators have completely recovered or one of them has not completely recovered; Effective: The condition improved after treatment and 2 to 4 of the four indicators still have not fully recovered; Invalid: After 3 d of imipenem treatment, the condition did not improve significantly and the lung signs even worsened.

Total effective rate=(Cure+Markedly effective+Effective)/Total cases

Acute Physiology and Chronic Health Evaluation II (APACHE II), blood gas analysis index:

The attending physician scored both groups APACHE II before treatment, 3 d and 7 d after treatment. A higher score evaluated the condition was more serious, APACHE II score >15 points were diagnosed as severe

pneumonia patients; detected the blood gas analysis indexes (Partial Pressure of Oxygen (PaO_2), Partial Pressure of Carbon Dioxide ($PaCO_2$)) of both groups before treatment, 3 d and 7 d after treatment respectively, analyzed by AVL-OPANTI blood gas analyzer (AVL Scientific Corporation, Roswell, NM, USA).

Statistical methods:

Adopted Statistical Package for the Social Sciences (SPSS) 20.0 software to analyze enumeration data and measurement data. Expressed enumeration data by Percent (%) and comparison of both groups tested by χ^2. Measurement data (APACHE II score, PaO_2, $PaCO_2$, CRP, PCT and IL-6 concentration levels in serum, etc.,) conformed to normal distribution and homogeneity of variance, used ($\bar{x}\pm s$) to indicate them and tested by t. $p<0.05$ was considered to possess statistical significance.

RESULTS AND DISCUSSION

Both groups had no remarkable difference in age, gender and basic diseases, so it possessed no statistical significance ($p>0.05$), they possessed comparability as shown in Table 1.

Both groups had no remarkable difference in APACH II scores before therapy, so it possessed no statistical significance ($p>0.05$); After 3 d and 1 w therapy, APACH II scores were obviously lower than before therapy, but experimental group decreased more than control group, which was obviously different ($p<0.05$), so it possessed statistical significance ($p<0.05$), as shown in Table 2.

Both groups had no remarkable difference in arterial blood gas analysis PaO_2, $PaCO_2$ levels before therapy, so it possessed no statistical significance ($p>0.05$); after 3 d and 1 w therapy, both groups had remarkable difference in arterial blood gas analysis PaO_2, $PaCO_2$ levels, so it possessed statistical significance ($p<0.05$), as shown in Table 3.

Both groups had no remarkable difference in PCT, IL-6 and CRP levels before therapy, so it possessed no statistical significance ($p>0.05$); After 3 d and 1 w therapy, compared PCT, IL-6 and CRP levels of both groups, experimental group had bigger downtrend than control group, which was remarkably different, so it possessed statistical significance ($p<0.05$). As shown in Table 4.

After 1 w therapy of both groups, total clinical effective rate of experimental group (91.4 %) was remarkably higher than control group (71.4 %), which was remarkably different, so it possessed statistical significance ($p<0.05$). As shown in Table 5.

TABLE 1: COMPARISON OF GENERAL INFORMATION OF BOTH GROUPS

	Experimental group (n=35)	Control group (n=35)	t/ ²	p
Age	62.8±8.04	62.22±8.64	0.29	0.77
Female	18 (51.4 %)	16 (45.7 %)	0.23	0.63
Complication			0.09	0.76
Hypertension	14 (40 %)	16 (45.7 %)	0.23	0.63
Diabetes	11 (31.4 %)	10 (28.6 %)	0.07	0.79
Chronic obstructive pulmonary disease	4 (11.4 %)	5 (14.3 %)	0.13	0.72

TABLE 2: COMPARISON OF APACH II SCORES OF BOTH GROUPS BEFORE AND AFTER THERAPY

Group	Cases	APACHE-II scores		
		Before therapy	3 d after therapy	7 d after therapy
Experimental group	35	28.31±8.17	16.71±3.41	12.77±3.41
Control group	35	27.65±7.06	19.85±2.78	16.05±3.28
t		0.36	-4.22	-4.08
p value		0.71	0.001	0.001

TABLE 3: COMPARISON OF ARTERIAL BLOOD GAS ANALYSIS PaO_2, $PaCO_2$ LEVELS OF BOTH GROUPS BEFORE AND AFTER THERAPY

Group	Cases	PaO_2			$PaCO_2$		
		Before therapy	3 d after therapy	7 d after therapy	Before therapy	3 d after therapy	7 d after therapy
Experimental group	35	58.78±8.07	68.68±4.82	74.22±8.05	48.57±19.29	35.11±15.01	26.02±9.83
Control group	35	58.34±12.88	62.34±8.88	68.4±0.94	48.71±13.67	41.62±12.67	37.91±10.82
t		0.005	3.71	3.31	-0.03	-1.98	-4.81
p value		0.95	0.004	0.001	0.97	0.05	0.000

TABLE 4: COMPARISON OF PCT, IL-6, CRP OF BOTH GROUPS BEFORE AND AFTER THERAPY

Group	Cases	PCT (ug/l)			IL-6 (pg/ml)			CRP (mg/l)		
		Before therapy	3 d after therapy	7 d after therapy	Before therapy	3 d after therapy	7 d after therapy	Before therapy	3 d after therapy	7 d after therapy
Experimental group	35	18.02±5.94	9.82±3.37	1.87±1.18	227.54±70.04	76.8±24.4	23.31±11.5	89.09±32.60	52.31±15.4	10.88±2.8
Control group	35	17.44±6.68	13.7±4.45	3.33±2.44	225.54±91.69	92.5±36.5	34.4±16.4	88.54±38.08	67.7±22.4	23.02±10.1
t		0.38	-4.21	-3.12	0.10	-2.12	-3.29	0.06	-3.53	-6.79
p		0.70	0.007	0.002	0.91	0.03	0.002	0.94	0.001	0.000

TABLE 5: COMPARISON OF CLINICAL EFFICACY OF BOTH GROUPS

	Cure+markedly effective	Effective	Invalid	Total effective rate
Experimental group	17 (48.6 %)	15 (42.9 %)	3 (8.6 %)	32 (91.4 %)
Control group	13 (37.1 %)	12 (34.3 %)	10 (28.6 %)	25 (71.4 %)
^{2}				4.63
p				0.03

Severe pneumonia is a systemic inflammation that can cause acute respiratory distress syndrome in critically ill patients, which develops rapidly and even death[13]. Common microbial infections include bacterial, fungal and viral infections and some of them are co-infections. Usually the released toxins and inflammatory factors can cause lung infections or systemic inflammatory reactions after entering the blood[14]. Patients with severe pneumonia generally receive symptomatic treatment such as antiviral treatment, anti-infection treatment and maintaining internal environment stability. In this treatment process, timely and effective oxygen therapy is essential. Patients usually require broad-spectrum anti-infective therapy and then further adjust to targeted anti-infective therapy based on the results of microbial testing[15]. Therefore, it is important to determine the type of microbial infection that causes severe pneumonia. Imipenem/cilastatin sodium is a fixed combination of imipenem (semi-synthetic carbapenem β-lactam antibiotic) and cilastatin sodium, the latter stops the renal metabolism of imipenem through a specific and reversible dehydropeptidase I inhibitor, dehydropeptidase I inactivates imipenem by hydrolyzing β-lactam ring[16]. Imipenem can penetrate the outer membrane of most gram-negative bacteria, compared with currently available β-lactam antibiotics, it is easier to enter Penicillin Binding Proteins (PBPs) *in vitro*, some researches have indicated that imipenem may have post-antibiotic inhibitory effects on some susceptible organisms[17]. Some people thought that it was a kind of beneficial effect, because during the dosing interval, imipenem may prevent the regeneration of susceptible organisms when the drug concentration at the infected site is lower than the minimum inhibitory concentration. The sensitivity of imipenem/cilastatin to *Enterobacter cloacae* was 96 %, *Escherichia coli* was 98 %, *Klebsiella pneumoniae* was 94 % and *Pseudomonas aeruginosa* was 36 %, so it has good anti-infection effect[18].

The course of severe pneumonia is closely related to the development of inflammatory factors. In the initial

stage of pneumonia, alveolar macrophages generate plenty of pro-inflammatory cytokines, for example IL-6, it can attract and activate polymorphonuclear leukocytes, which are necessary for local bacterial defense and elimination, IL-6 has also been defined and evaluated as one of the most distinctive markers of recovery in pneumonia patients, severe pneumonia has higher serum IL-6 levels than mild pneumonia[19]. CRP is a recognized inflammatory marker. It is an inflammatory factor and a sensitive indicator for diagnosing chronic inflammation. It is significantly increased in tissue damage and acute inflammation and is a sign of inflammatory response. Many studies have shown that PCT has a high degree of sensitivity and specificity for the early identification of non-infectious Systemic Inflammatory Response Syndrome (SIRS) and sepsis[20]. With the use of antibiotics, the concentration of PCT decreases, therefore, it can fully monitor infection evolution and help adjust the duration of antibiotic use. Furthermore, the relationship between PCT and microbial etiology has always been a controversial issue[21]. Some studies have reported that gram-negative bacteremia have higher PCT levels than gram-positive bacteremia and fungal infections. This study also confirmed that imipenem can effectively reduce inflammatory markers levels in the serum.

In this study, we discussed imipenem on treating severe pneumonia. The clinical treatment efficiency of patients after imipenem treatment was significantly higher than control group ($p<0.05$). After 3 d and 1 w therapy, APACH II scores and $PaCO_2$ of experimental group had bigger downtrend than control group, but PaO_2 had faster uptrend than control group, which was remarkable different, so it possessed statistical significance ($p<0.05$). After 3 d and 1 w therapy, compared PCT, IL-6 and CRP levels of both groups, experimental group had bigger downtrend than control group, which was remarkably different ($p<0.05$). Total clinical effective rate of experimental group (91.4 %) was remarkably higher than control group (71.4 %), which was remarkably different. It is suggested that imipenem can significantly improve the clinical effective rate of severe pneumonia, reduce the concentration of serum PCT, CRP and IL-6, and provide clinical guidance value for the effective treatment of severe pneumonia.

Authors' contributions:

Junzhong Ke and Jinchao Mao have contributed equally to this work.

Conflict of interests:

The authors declared no conflicts of interest.

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