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“Impact of pentaglobin in severe COVID 19 pneumonia- a prospective study.”

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ABSTRACT

Background: The current COVID-19 pandemic has become a global public health crisis and presents a serious challenge in treatment of severe COVID pneumonia patients. With an imperative need for an effective treatment, we aimed to study the effectiveness of Pentaglobin, an intravenous immunoglobulin in the treatment of severe Covid-19 pneumonia patients.

Methods: This is an open-label non-randomised controlled study. Patients in the study group (n = 17) received Pentaglobin in addition to standard therapy and the control group (n = 19) received only the standard of care treatment. Severity of illness were quantified by severity scores and inflammatory laboratory parameters were compared between the two groups.

Results: The average length of hospital stay in pentaglobin group were 12.35 ± 6.98 days compared to 10.94 ± 4.62 days in standard treatment group with mean difference of 1.4 days (p value = 0.4). Pentaglobin did not provide an added advantage in terms of reducing the duration of hospital stay. There was no significant difference between both the groups in terms of requirement of invasive ventilation (p = 0.56) and mortality (p = 0.86). CT Severity score (OR = 1.39 95% CI = 1.09–1.77, P = 0.01), APACHE II score (OR = 1.16 95% CI = 0.99–1.35, P = 0.05) and the SOFA score (OR = 2.11 95% CI = 1.13–3.93, P = 0.02) were independent predictors of mortality.

Conclusion: The administration of pentaglobin in COVID-19 patients has no significant effect in reducing the risk of mechanical ventilation or death, in disease worsening or in reduction of inflammation.

1. Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 in Wuhan, China as the cause of a respiratory illness designated coronavirus disease 2019, or Covid-19 [1]. As of 24 March 2021, more than 124 million cases have been confirmed, with more than 2.74 million deaths attributed to COVID-19 [2]. Several therapeutic agents have been evaluated for the treatment of Covid-19 and trials are ongoing [3]. There are increasing evidence that SARS-CoV-2 infection triggers massive influx of activated immune cells to the lungs which leads to a systemic inflammatory response syndrome in Covid 19 pneumonia. As this inflammatory response is the major cause of morbidity and mortality, drugs targeting inflammation have gained much interest [4]. Pentaglobin is a commercially available intravenous immunoglobulin specifically enriched with immunoglobulin (IgM) and it has been reported as a relevant immunomodulant therapy in several infectious diseases, with improvement in clinical course of the illness [5]. We hypothesized that early intervention with pentaglobin in severe Covid-19 pneumonia patients, might limit the progression to hypoxemic respiratory failure or death and reduce the risk of clinical worsening.

2. Materials and methods

2.1. Study design and treatment protocol

This is an open-label non-randomised controlled study conducted in a tertiary cardiac care hospital caring COVID-19 patients. The study was done after obtaining institutional ethics committee approval. The patient’s details with full medical history, chronic comorbidities, demographic and epidemiological data were obtained on admission. Informed consent to participate in the study was obtained. Patients ≥ 18 years of age with severe COVID-19 pneumonia documented by positive Reverse transcription polymerase chain reaction (RT-PCR)
nasopharyngeal swab or with a CT-chest showing evidence of ground glass opacity requiring high dependency unit admission were considered eligible for the study. Clinical data, including symptoms, baseline temperature, chest x-ray, complete blood count, coagulation parameters, inflammatory and biochemical markers were obtained. The following were considered as inclusion criteria 1) SpO2 < 94% while breathing ambient air.2) the need for mechanical ventilation 3) tachypnea with respiratory rate ≥ 28 breaths per minute. Exclusion criteria included 1) known hypersensitivity reactions to human immunoglobulin 2) pregnant/breast feeding women 3) End stage renal disease 4) chronic liver disease (child pugh C 5) Glasgow coma scale < 8 on admission. Thirty six patients were enrolled and were divided into 2 groups, the intravenous immunoglobulin (IVIG) group and the control group. The IVIG group (17 cases) were treated with IVIG enriched with IgM (Pentaglobin, Biostest AG, Dreieich, Germany) in addition to standard of care treatment according to the regional COVID-19 guidelines. 5 ml/kg/day of Injection Pentaglobin® (38 g/IgG, 6 g/IgM and 6 g/IgA) was started as an intravenous infusion over a period of 6 h on the day of admission to ICU after confirmation of COVID –19 pneumonia, and repeated for 3 consecutive days. The control group (19 cases) were treated only with standard of care treatment. Injection Remdesivir was administered intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily for next 4 days. In addition, all patients received oxygen supply to target SpO2 reaching >95%, Azithromycin 500 mg once per day for 5 days, IV antibiotics at the physician’s discretion when suspecting a bacterial respiratory superinfection, Dexamethasone 6 mg daily for 10 days, Vitamin C 1 gm daily and low molecular weight heparin for prophylaxis of deep vein thrombosis according to bodyweight and renal function.

3. Clinical severity and radiological assessment

The severity of illness were assessed using Subsequent Organ Failure Assessment (SOFA) score, Acute physiology and chronic health evaluation II (APACHE II) score, Simplified acute physiology score II (SAPS II) score and quick covid –19 severity index score (q CSI) launched during the COVID 19 pandemic. Mental status of all patients were assessed using Glasgow coma scale. The chest CT-severity score (CTSS) was defined by summing up individual scores from 20 lung regions, with the physician’s discretion when suspecting a bacterial respiratory superinfection, and those treated with standard of care alone in terms of demographics and clinical parameters. Quantitative variables were expressed as mean ± standard deviation and qualitative variables were expressed as number percentage. Categorical variables were compared using the Chi-square test. Comparison of parametric values between groups were performed using the independent sample t-test. Logistic regression analysis was performed to predict the mortality, while linear regression was used to predict the length of hospital stay. A nominal significance was taken as a two-tailed P < 0.05.

4. Results

Table 1 represents the baseline characteristics of the study population in both group. The mean age of the study population was 67.39 ± 11.44. Male to female ratio was 7:2 in the total population. 44% of the study group had hypertension, 47% had diabetes and 22% had history of coronary artery disease. One patient in the pentaglobin group had hypothyroidism along with morbid obesity, while one patient in the standard treatment only group had Parkinson disease. Average Acute

| Characteristics | Overall (N = 36) | Pentaglobin plus standard care group(N = 17) | Standard care only group (N = 19) | P value |
|-----------------|-----------------|---------------------------------------------|-----------------------------------|---------|
| Age (years)     | 67.39 ± 11.44   | 66.12 ± 12.95                               | 68.53 ± 10.13                    | 0.536   |
| Male            | 28 (77.78%)     | 16 (94.1%)                                  | 12 (63.2%)                       | 0.07    |
| Female          | 08 (22.22%)     | 01 (5.9%)                                   | 07 (36.8%)                       |         |
| Hypertension    | 16 (44.44%)     | 07 (41.2%)                                  | 09 (47.4%)                       | 0.97    |
| Diabetes        | 17 (47.22%)     | 10 (58.8%)                                  | 07 (36.8%)                       | 0.32    |
| CAD             | 08 (22.22%)     | 02 (11.8%)                                  | 06 (31.6%)                       | 0.30    |
| Other comorbidities | 02 (5.56%)   | 01 (5.9%)                                   | 01 (5.3%)                        | 0.63    |
| Temperature (°F) | 101.49 ± 1.66   | 102.06 ± 1.52                               | 100.99 ± 1.66                    | 0.60    |
| GCS O/A         | 14.56 ± 0.77    | 14.53 ± 1                                   | 14.58 ± 0.51                     | 0.851   |
| APACHE II score | 11 ± 5.44       | 11.94 ± 6.13                                | 10.16 ± 4.75                     | 0.33    |
| SAPS II score   | 2.52 ± 1.5      | 2.59 ± 1.73                                 | 2.47 ± 1.31                      | 0.823   |
| q - CSI score   | 7.69 ± 3.00     | 7.41 ± 3.48                                 | 7.95 ± 2.57                      | 0.6     |
| WBC (cells/mm³) | 11946.94 ± 6585.92 | 14854.70 ± 4945.43 | 9345.26 ± 6889.77 | 0.01 |
| D-dimer (ng/ml) | 1973.22 ± 2032.33 | 2530.23 ± 2642.26 | 1474.84 ± 1127.09 | 0.12 |
| Troponin (mg/ml)| 61.65 ± 119.15  | 26.25 ± 33.30                               | 93.34 ± 156.08                   | 0.09    |
| CRP (mg/l)      | 98.43 ± 76.48   | 102.69 ± 85.13                              | 94.62 ± 69.99                    | 0.75    |
| IL6 (pg/ml)     | 249.18 ± 372.01 | 379.58 ± 497.04                            | 132.51 ± 138.13                  | 0.04    |
| Ferritin (ng/ml)| 467.16 ± 371.28 | 569.88 ± 454.39                            | 375.25 ± 256.18                  | 0.118   |
| CT Severity score | 25.19 ± 4.16    | 24.88 ± 4.31                                | 25.47 ± 4.12                     | 0.67    |
| Require O2 on admission | 14 (38.89%) | 04 (23.5%)                                  | 10 (52.63%)                      | 0.07    |
| Require NIV on admission | 22 (61.11%) | 13 (76.47%)                                  | 09 (47.37%)                      | 0.07    |

GCS O/A denotes glasgow coma scale on admission, Subsequent Organ Failure Assessment (SOFA) score, Acute physiology and chronic health evaluation II (APACHE II) score, Simplified acute physiology score II (SAPS II) score and quick covid –19 severity index score (q CSI), IL-6 denotes serum interleukin-6, CRP denotes C reactive protein, Non-invasive ventilation (NIV) includes nasal high flow oxygen therapy, noninvasive positive pressure ventilation (NIPPV), or both.

3.1. Primary and secondary outcome

The primary outcome of the study was to evaluate the efficacy in terms of mortality, duration of length of hospital stay and need of invasive ventilation. The indications for mechanical ventilation were defined by the presence of respiratory distress with activation of accessory respiratory muscles, the need for FiO2 of 80% or more to maintain a SaO2 level of 90%, or a PaO2/FiO2 ratio of <200 mm Hg. The secondary outcomes were to 1) evaluate fall in the inflammatory marker levels on day 5 post treatment with pentaglobin.2) parameters predicting longer hospital stay and mortality among the study groups.

3.2. Statistics

The data analysis was done with “IBM SPSS version 22” (IBM Corp., New York, USA). All the data were collected on a set data sheet and variables entered into a common database for analysis. We compared
the duration of hospital stay in patients who survived, but this difference was 4.84 days with a mean difference of 9.75 days (95% CI 1.39, 9.75 – 0.86). There was no significant difference between both the groups in duration of hospital stay in the pentaglobin group. The difference between lab parameters like D-dimer (P = 0.42), Troponin-I (P = 0.009), C- reactive protein (CRP) (P = 0.72), and ferritin (P = 0.118) were found non-significant in both the groups. Average CT severity score was calculated at 25.19 ± 4.16 with no significant difference of the study population required supplemental oxygen, with 4 patients (23.5%) in the pentaglobin group and 10 patients (52%) in the standard treatment group (p = 0.07). Further, 22 patients (61%) required non-invasive positive pressure ventilation (NIPPV) support with 13 patients (76.4%) patients in the pentaglobin group and 9 patients (47.3%) patients in the standard treatment group (p = 0.07). There were no adverse events, significant alterations in liver function, renal function or haemolytic anaemia observed with pentaglobin infusion.

Table 2 shows the Primary outcomes of the study population. The average length of hospital stay in pentaglobin with standard treatment group was 12.35 ± 6.98 days compared to 10.94 ± 4.62 days with mean difference of 1.4 days between the study groups (p value = 0.4). Pentaglobin did not provide an added advantage in terms of reducing the duration of hospital stay. Among survivors, mean duration of length of hospital stay was 10.76 ± 4.50 days, with pentaglobin group staying 9.75 ± 4.26 days and the standard treatment group staying 11.64 ± 4.84 days with a mean difference of 1.89 days. Pentaglobin reduced the duration of hospital stay in patients who survived, but this difference was not clinically significant (p = 0.3). Among non survivors, the mean duration of hospital stay in the pentaglobin was 18.6 ± 8.70 days and that of standard treatment only group was 9 ± 3.67 days with a mean difference of 9.6 days (p value = 0.05) implying an early mortality than pentaglobin group patients. 30% of study population required invasive ventilation with 5 patients (29%) in pentaglobin group and 6 patients (31.5%) in the standard treatment only group (p = 0.56). 10 patients (27.8%) of the study population expired with 5 patients in each group (p = 0.86). There was no significant difference between both the groups in terms of requirement of invasive ventilation and mortality.

Table 3 lists the predictors of mortality. CT Severity score (OR = 1.39, 95% CI = 1.09–1.77, P = 0.01), APACHE II score (OR = 1.16, 95% CI = 0.99–1.35, P = 0.05) and the SOFA score (OR = 2.11, 95% CI = 1.13–3.93, P = 0.02) significantly predicted mortality in the study group. Other scores and the levels of inflammatory markers on admission were not found as a significant predictors of mortality. qCSI score had a good prediction of hospital stay (OR = 1.22, 95% CI = 0.46–1.54, P = 0.001).

Table 4 shows the comparison of severity scores and lab parameters between survivors and non-survivors. APACHE II score, SOFA score, SAPS II score, D-dimer and CTSS were significantly higher in the non-survivor groups in comparison to survivors. The inflammatory markers and the leukocyte count collected on the day of admission and day 5 of both the groups were analysed. In the pentaglobin with standard care treatment group, the mean IL-6 levels, CRP, total leukocyte counts and the serum ferritin levels decreased on day 5 after admission, but the decrease was not clinically significant. In the standard treatment only group, the CRP levels on admission were 94.62 ± 69.99 and decreased significantly on day 5 to 37.98 ± 53.99 with a mean difference of –56 (p < 0.01). Total leucocyte counts on admission were 9345.26 ± 6899.77 and day 5 were 11335.26 ± 4753.52 with a mean difference of 190. The increase in the leukocyte count was non-significant (P = 0.33). The mean IL-6 levels and serum ferritin levels decreased on day 5 from admission, but the difference was not significant presented in table 5. Comparison of mean difference of lab parameters, pre and post treatment between the Pentaga group and standard care only group showed that fall in leucocyte count in Pentaga group was significant (p = 0.03).

### Table 2
Hospital stay in both the groups.

| Characteristics | Total (N=36) | Pentaglobin plus standard care group (N=17) | Standard care only group (N=19) | Mean Difference | 95 %CI | P value |
|-----------------|-------------|---------------------------------------------|-------------------------------|----------------|-------|--------|
| **Length of hospital stay (mean number of days)** | | | | | | |
| Survivors | 11.61 ± 5.73 | 12.35 ± 6.98 | 10.94 ± 4.62 | 1.4 | -2.57 to 5.38 | 0.4 |
| Non survivors | 10.76 ± 4.50 | 9.75 ± 4.26 | 11.64 ± 4.84 | -1.89 | -5.61 to 1.83 | 0.3 |
| **Required invasive ventilation (%)** | 11 (30.56%) | 05 (29.4%) | 06 (31.58%) | | | 0.56 |
| **Mortality (%)** | 10 (27.8%) | 05 (29.4%) | 05 (26.3%) | | | 0.86 |

### Table 3
Regression analysis for mortality and Hospital stay.

| Variables | OR (95% Confidence intervals)/95% CI | P value |
|-----------|---------------------------------------|---------|
| **Mortality** | | |
| CTSS | 1.39 (1.09–1.77) | 0.01 |
| APACHE II | 1.16 (0.99–1.35) | 0.05 |
| SOFA | 2.11 (1.13–3.93) | 0.02 |
| qCSI | 1.02 (0.92–1.38) | 0.174 |
| SAPS II | 1.06 (0.98–1.13) | 0.09 |
| D dimer | 1 (1–1.001) | 0.06 |
| CRPQ | 1.003 (0.99–1.01) | 0.52 |
| IL6 | 1 (0.99–1.02) | 0.298 |
| Ferritin | 1 (0.99–1.03) | 0.264 |

| Variables | Survivors | Non survivors | P value |
|-----------|-----------|---------------|---------|
| **Age (years)** | 67.50 ± 11.02 | 67.10 ± 11.10 | 9.927 |
| APACHE II | 9.81 ± 3.91 | 14.10 ± 7.61 | 0.032 |
| SOFA | 2.11 ± 1.31 | 3.89 ± 1.31 | 0.016 |
| qCSI | 7.27 ± 2.85 | 8.80 ± 3.26 | 0.174 |
| SAPS II | 23.38 ± 7.36 | 33.30 ± 21.66 | 0.045 |
| WBC (cells/mm³) | 16977.69 ± 5216.47 | 14467 ± 9121.97 | 0.157 |
| D dimer (ng/ml) | 1511.54 ± 1305.75 | 3173.61 ± 3018.24 | 0.026 |
| Troponin (ng/ml) | 49.26 ± 105.75 | 93.90 ± 150.19 | 0.321 |
| CRP (mg/l) | 93.40 ± 78.34 | 115.11 ± 73.74 | 0.532 |
| IL-6 (pg/ml) | 292.06 ± 423.55 | 137.70 ± 144.15 | 0.271 |
| Ferritin (ng/ml) | 425.33 ± 359.59 | 581.15 ± 396.14 | 0.259 |
| CTSS | 23.54 ± 3.76 | 28.70 ± 4.16 | 0.001 |
Table 5
Comparison of lab parameters on admission and Day 5 post treatment between study groups.

| Parameters | Pentaglobin plus standard care group (n = 17) | Standard care only group (n = 19) | p value
|------------|---------------------------------------------|----------------------------------|-------|
|            | On admission  | Day 5 post treatment | Mean difference | p value | On admission  | Day 5 post treatment | Mean difference | p value |
| IL6 (pg/ml) | 379.58 ± 497.04 | 278.47 ± 309.44 | -101.11 | 0.46 | 132.51 ± 138.15 | 100.45 ± 72 | -32.06 | 0.37 |
| WBC (cells/mm³) | 14854.70 ± 541.11 | 12295.88 ± 85.13 | -2595 | 0.14 | 9345.26 ± 569.88 | 11335.26 ± 88.41 | 1990 | 0.33 |
| CRP (mg/l) | 509.68 ± 454.39 | 51.05 ± 8.51 | -51.64 | 0.09 | 94.62 ± 69.99 | 37.98 ± 53.99 | -56.64 | 0.01 |
| Ferritin (ng/ml) | 206.24 ± 138.15 | 511.84 ± 51.64 | -30.06 | 0.84 | 375.25 ± 256.18 | 354.39 ± 206.24 | -20.06 | 0.78 |

P value* denotes comparison between Pentaglobin group with standard care only group

5. Discussion

The COVID – 19 pandemic has become a great challenge for physicians currently. There are no uniform treatment guidelines for this disease at present. Most of the treatment options used are investigational, with efficacy clearly not proved [6]. Evidence suggests that the pathophysiological basis of profound decline in clinical status in these patients is due to a severe inflammatory response resembling cytokine release syndrome [7]. In this period, patients have markedly abnormal inflammatory markers like elevated serum interleukin-6, ferritin, and C-reactive protein levels. Intravenous immunoglobulins (IVIG) have been shown to be beneficial in the treatment of many autoimmune and inflammatory conditions. In vitro data suggest that cytokine modulation might be responsible for the therapeutic efficacy of IVIg [8]. Pentaglobin is a human IgM-enriched IV immunoglobulin. One ml solution contains human plasma protein 50 mg which is composed of immunoglobulins with IgM (6 mg), IgA(6 mg), IgG (38 mg) along with other constituents like glucose monohydrate and sodium chloride. Pentaglobin should be stored in refrigerator (-2°C to +8°C) and should be warmed to room or body temperature before use. After intravenous administration, immunoglobulins are immediately and completely available in recipient circulation [9]. IVIG and pentaglobin have been shown to be more effective than IVIG in preventing complement deposition in vitro, and IVIGM was shown to be more effective than IVIG in inhibiting complement deposition in the rat anti-Thy 1 nephritis model [10]. Pentaglobin has been earlier studied and found to be a promising adjuvant therapy in patients with severe sepsis and septic shock [11,5,12,13], in neonatal sepsis [14], as a prophylactic agent for reduction of endotoxemia in bone marrow transplant recipients[15,16], as prophylaxis or as adjunct treatment for acute graft-versus-host disease [17], in reduction of myocardial inflammation in parvovirus b19 associated myocarditis [18]. Pentaglobin has also been previously studied in steroid resistant severe acute respiratory syndrome and was shown effective and safe in treating these patients [19]. No data are yet available on the treatment of Covid-19 with Pentaglobin. Recently, there are reports stating that early usage of pentaglobin in COVID-19 pneumonia for 3 consecutive days can benefit by slowing down the cytokine hyperactivation and induce immunological support in the healing of COVID-19 pneumonia [20]. To the best of our knowledge, our study is the first trial that evaluated the effectiveness of pentaglobin in patients with severe COVID-19 pneumonia. This present study showed that pentaglobin in addition to standard treatment was not associated with clinical improvement in severe COVID-19 pneumonia patients. Pentaglobin did not decrease the need for invasive ventilation, not associated with decrease in the length of hospital stay and is not associated with mortality benefit. Welte et al in a randomised, placebo controlled phase II trial investigated on use of another novel human polyclonal antibody preparation (trimodulin) containing ~ 22% immunoglobulin (Ig) M, ~ 21% IgA, and ~ 56% IgG as add-on therapy for 160 patients with severe community acquired pneumonia (sCAP) and found that there was no statistically significant difference in VFDs and mortality between trimodulin and placebo. However, they did a Post hoc analyses which supported improved outcome regarding mortality with trimodulin in subsets of patients with elevated CRP and reduced IgM [21].

Routine use of validated scoring systems like APACHE II and SOFA score can be useful in categorising high risk patients and in predicting the mortality risk in severely ill patients. The new q CSI score has only 3 variables like pulse oximetry, respiratory rate and oxygen flow rate in L/min can help in triaging patients and in prediction of hospital stay. Covino et al, in a cohort of confirmed COVID-19 patients compared the three specifically developed Covid 19 scores like ISARIC – 4C score, q CSI and COVID GRAM score showing that all scores showed a fairly good predictive value with respect to in-hospital death [22]. The CT Severity score was found as an independent predictor of mortality in our study with odds ratio of 1.39 [95% CI: 1.09–1.77]. Tabatabaei SM et al demonstrated that CT severity score is a reliable predictor of mortality with a score more than 7.5 having a sensitivity of 83% in predicting mortality in nonelderly previously healthy individuals with COVID-19 pneumonia [23]. Although, our study showed that the fall in inflammatory markers occurred in both pentaglobin plus standard treatment group and standard treatment only group, the differences were statistically insignificant and do not support the hypothesis that pentaglobin reduces inflammatory markers progressively.

6. Limitations

Interpretation of the results of this study is limited by the small size of the cohort and the lack of randomisation. There are ongoing trials in other centres to study the effect of pentaglobin in critically ill COVID-19 patients, which may further add knowledge to our study.

7. Conclusion

The administration of pentaglobin in COVID – 19 patients had no significant effect on reducing the risk of mechanical ventilation or death, on disease worsening or in reduction of inflammation. A large prospective randomized trial is warranted to further evaluate the role of pentaglobin as an adjunctive therapeutic strategy for COVID – 19 pneumonia.

CRediT authorship contribution statement

Dinesh Joshi: Conceptualization, Methodology, Investigation. Kamal Sharma: Conceptualization, Methodology, Investigation. Senthilraj Thangasami: Conceptualization, Methodology, Investigation. Rahul Patel: Data curation. Iva Patel: Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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