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**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.1413638>Available online at: <http://www.iajps.com>**Research Article****COMBINATION OF INTRAVENOUS IMMUNOGLOBULIN
AND STEROID PULSE THERAPY IMPROVES OUTCOME OF
FEBRILE REFRACTORY STATUS EPILEPTICUS**¹Dr. Amna Tahir,²Dr. Iqra Liaqat,³Dr. Khaija Salman¹EMO, Indus Hospital, Manawan, Lahore.²WMO, BHU 285JB, Gojra.³WMO, Indus Hospital, Manawan, Lahore.**Abstract:**

In pediatric refractory epileptic, the febrile infections play an important role; accordingly inflammatory processes and mechanisms of immune-mediated have been linked with neurological symptoms in such cases. The basic aim of the study was to analyze the immunotherapy impacts as the adjuvant medication of febrile refractory epilepticus.

We adopt different cases of "febrile refractory status epilepticus" for retrospective revision through a pediatric ICU (intensive care unit) from the period of Jan 2000 to Dec 2013 and assessed all clinical features. Those cases were excluded in which antineuronal antibodies were positive against surface antigens.

Sixty-three patients enrolled (through which 38 boys have age between 1 to 18 years) all boys obtained different antiepileptic drugs. We found that 29 patients (which was 46%) obtained intravenous immunoglobulin and 16 patients (25.4%) received a blend of methylprednisolone pulse and intravenous immunoglobulin therapy and finally 18 patients (28.3%) did not take any immunotherapy medication or treatment. Generally 12 (19%), patients died in a month. Twelve (20%) patients showed better neurological results, also including 2 who resumed to zero and 29.5% (13 patients) who had encouraging seizure results. We tried to explore and compare multiple treatments and established that methylprednisolone pulse therapy and intravenous immunoglobulin combination had the favorable seizure and neurological results in six months parallel with intravenous immunoglobulin alone without any immunotherapy.

Our study exclusively represented that methylprednisolone pulse therapy and intravenous immunoglobulin combination as an adjuvant is the best treatment for "febrile refractory status epilepticus" and linked with better seizure and neurological results. As there is no end in research additional prospective researches are required for confirmation of these findings.

Keywords: *Methylprednisolone, intravenous immunoglobulin, pediatric, refractory status epilepsy, neurological outcomes*

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1.0 INTRODUCTION:

“Refractory status epilepticus” is a tenacious seizures state which lasts more than two hours despite optimum treatment of antiepileptic drugs. Refractory status epilepticus is basically a neurological emergency which further causes high neurological sequelae. In some cases, the severity of these stark may cause death. It is found that there are multiple causes of “pediatric refractory status epilepticus” and some are related to febrile. Inflammatory processes and immune-mediated mechanisms are a main role player in contributing and determining to the manifestations of neurological in affected patients (Jain and Harvey, 2012).

However, it is very difficult to distinguish the aetiology at the initial stage of one or two days of refractory status epilepticus. About the pathogenesis, highly increasing indication advises that inflammation of acute brain may incline through fever while status epilepticus can further lead to continues brain nervousness, which may further interpose to refractory epilepticus status. Additionally, continuous refractory status epilepticus persuaded inflammation of the chronic brain and interpose to epileptogenesis. Finally, it was also observed that brain inflammation is initiated by interleukin-1 activation (John, 2006).

Therefore, researches confirm that the use of methylprednisolone pulse therapy and IVIG (intravenous immunoglobulin) treatment of “febrile status epilepticus” are wanting and some of the cases published only. Aggressively application of methylprednisolone pulse therapy and IVIG in patients may expedite a highly stauncher recovery, but it continuously indistinct that a blend of methylprednisolone pulse and IVIG therapy is better to IVIG only (KUMAR and BLECK, 2005).

2.0 MATERIAL AND METHODS:

In this study, we retrospectively revised pediatric patients who admitted to pediatric ICU and diagnosed with “refractory status epilepticus”, specifically between Jan 2000 till Dec 2013. The additional case ascertainment criteria were formerly children with good health and a “febrile refractory status epilepticus” diagnosis (Jain and Harvey, 2012). Patients over 18 years of age have been excluded, those also exclude who have no fever, those also exclude who have bacterial meningitis, and similarly, those also excluded who have some history of neurological disorders or neurological insults,

hypoglycaemia, and electrolyte imbalance. All those patients also excluded from positive antineuronal antibodies contrary to surface antigens and all those that have immunotherapies; like a blend of dexamethasone and IVIG, rituximab, methylprednisolone, and plasmapheresis (Matsukuma *et al.*, 2018).

All treatment, clinical features, and results were specifically recorded and the patients have been divided into three categories:

All those patients who took methylprednisolone pulse therapy and IVIG combination

All those patients who received only IVIG

And those who never took immunotherapy

The basic results were a seizure and neurological outcomes after a half year of evaluation. Hospital course was the secondary outcome with the addition of pediatric ICU, hospitalization duration and the rate of one month’s mortality. After the initial status epilepticus episode after six months seizure and neurological results were resolute. Similarly, “Pediatric Cerebral Performance Score” was the main source of evaluation of neurological outcomes. The “Pediatric Cerebral Performance Score” defined as if there was ≤ 2 that was a good result while ≥ 3 considered a bad result. All the admitted patients basically treated with drugs of antiepileptic at their discharge (Rantsch *et al.*, 2011).

Outcomes of seizure were further categorized into 2 classes, with the strict follow-up of six months:

The first group is “intractable epilepsy” known as per month’s rate of seizures are two or this group’s patients taking two or more than two antiepileptic drugs;

The second group is “favorable result” known as seizure free or after treatment, they have lesser than two seizures in a month (Matsukuma *et al.*, 2018).

2.1 Statistical Assessment

The initial and secondary results were compared and assessed between those who took methylprednisolone pulse therapy and IVIG combination, who took IVIG alone and all those who never took immunotherapy. All descriptive data were shown as a percentage or SD (as a mean \pm standard deviation). The Kruskal-Wallis and Mann-Whitney *U* test were performed to achieve continuous variables and Fischer’s exact test was performed to achieve categorical variables (Rantsch *et al.*, 2011).

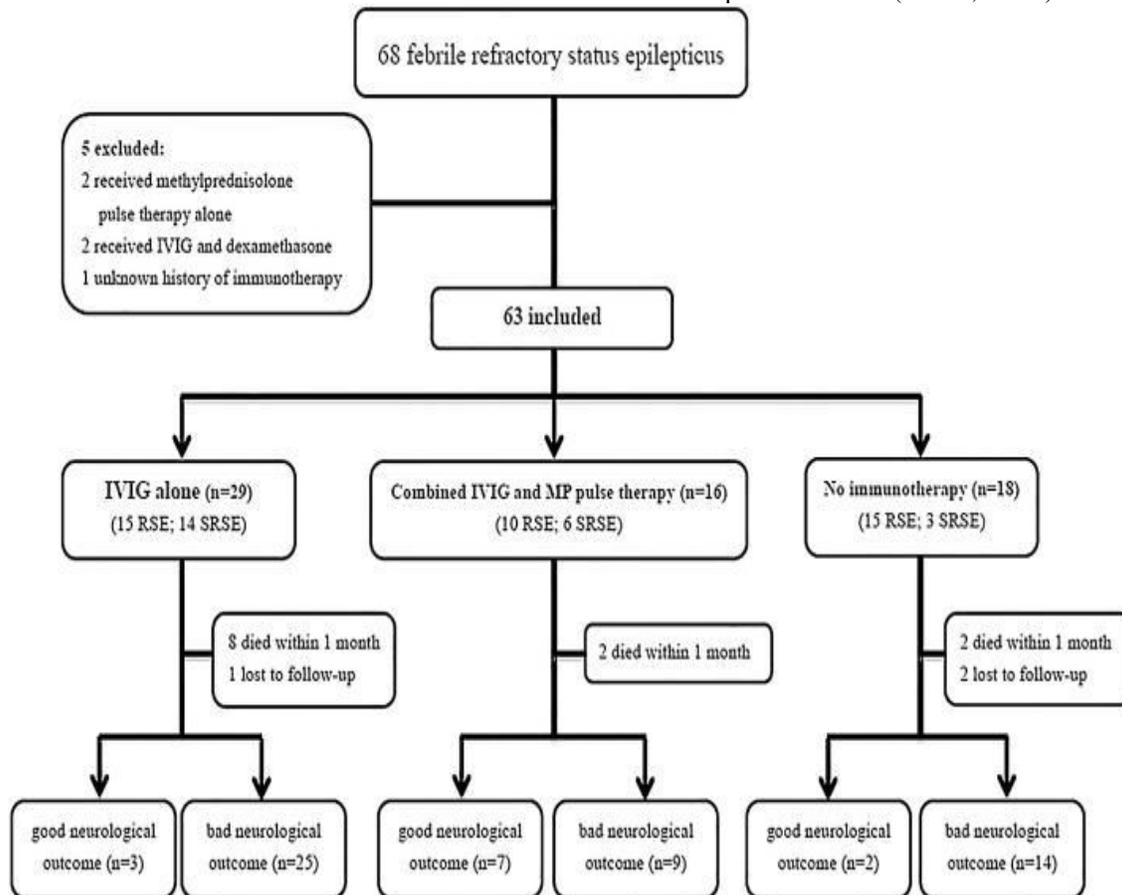
3.0RESULTS:

During the analysis period, sixty-eight formerly healthy children were identified who also have “febrile refractory status epilepticus” and those children were also admitted in pediatric ICU. Basically, sixty-three children were involved in this analytical study from those sixty-eight students (Reutlinger et al., 2010).

Those 63 further divided into (25 girls (the ratio was 39.7%) and 38 boys (the ratio was 60.3%) with a mean of (\pm standard deviation) age from 8.88 ± 5.11 years (the range started from 2 months till 18 years, but all children were below 18 years). As mentioned above 5 patients out of 68 were excluded, the classification of these five was: 2 took methylprednisolone pulse therapy as single medication, 2 patients took dexamethasone and IVIG combination and 1 patient had unclear immunotherapy history (Rantsch et al., 2011).

The mean period for our analytical study of “prior febrile infections” was 1 to 7 days (3.06 ± 2.0 days). In a blend of methylprednisolone pulse therapy and IVIG group (n=16), the basic types of seizure were simplified “tonic-clonic seizure” (31.2%; 5/16), and pivotal and primary pivotal with lesser simplified seizures (68.8%, 11/16). Furthermore, six of these sixteen (37.5%) children grew “super-refractory status epilepticus” which further need high-dosage of destructive coma therapy. In the group of IVIG (n=29) the basic types of seizure were simplified “tonic-clonic” seizures (20.7%; 6/29) and pivotal and primary pivotal lesser simplified seizures, 79.3%; 23/29 (Reutlinger et al., 2010).

From 29 children, 14 (48.2%) grew “super-refractory status epilepticus”. According to that group which did not take immunotherapy (n=18) the basic types of seizure were simplified “tonic-clonic” seizure (27.8%; 5/18) and pivotal and primary pivotal with lesser simplified seizures (72.2%; 13/18).



(Source: Lin et al., 2018)

According to figure 1, (already mentioned above also) 68 formerly healthy children were analyzed with “febrile refractory status epilepticus” in the period of this analytical study and from those 63 were included while 5 were excluded. Eight patients (27.6%) have died in a month in the IVIG group (n=29), similarly, 2 patients died and 1 patient lost to follow-up in this period. Three of all patients (with the ratio of 10.7% had a better neurologic result, while in the blend of IVIG and methylprednisolone pulse therapy group (n=16) 12.5% (two patients) died in one month, furthermore two more patients died during the period of follow-up. Seven other patients (with the ratio of 43.7%) had a better neurologic result (Lin et al., 2018).

3.1 Hospital Course, treatment and Outcome

All the patients established different antiepileptic drugs to manage their seizures. Additionally, all patients obtained acyclovir and empiric antibiotics prior to infectious aetiology were omitted, similarly, all of them were intubated with inotropic agents. In this analytical study, we consume the several anti-epileptic drugs for the cause of intensity of therapy. Analysis of the univariate represented that there is no the important relationship between outcome and anti-seizure therapy intensity *according to that the odds ratio = 1.207, which is 95% CI = 0.659-2.208, p = 0.542 (Lin et al., 2018).*

Forty-six percent (29) patients took only intravenous immunoglobulin while 25.4 (16) patients took methylprednisolone pulse therapy and intravenous immunoglobulin combination as adjuvant treatment and finally 28.6% (18) patient did not take any immunotherapy treatment. Accordingly, 12 patients (which are 19%) died within one month's period (Sabharwal et al., 2015).

All survivors (n=51) were released from the hospital with the anti-epileptic course of drugs. Among these patients, 27 children had re-admission according to un-managed seizures after the initial admission, with 4 child patients awarded with regular status epilepticus in the follow-up tenure (Sabharwal et al., 2015).

With the core follow-up period of six months, 4 patients died and 3 lost to the continuation. Twelve patients (which are 20% of the ratio) had better neurological results and 13 patients (which are 29.5%) had constructive seizure results. In the blending of methylprednisolone pulse therapy and

IVIG category, 7 patients (43.8%) had effective neurological result in six months period (there “Pediatric Cerebral Performance Score was \leq (2) with two who returned to zero. In one month period, two patients died while 2 died with the cause of sepsis during the tenure of follow-up (Shorvon, 2011).

3.2 Groups' Comparison (who took IVIG and methylprednisolone pulse therapy combination and that group who took only IVIG without immunotherapy)

In the combination of methylprednisolone pulse therapy and IVIG group, the patients had an expressively good seizure and neurological results within the period of six months as compared with no immunotherapy and IVIG alone group. Therefore, there was no important variance between immunotherapy group and IVIG alone group; in the seizure and neurological outcomes at six month's period. Additionally, IVIG and methylprednisolone pulse therapy combination group had also shown a lesser one-month mortality ratio as compared with IVIG alone group (12.5% compared with 27.6%). Accordingly, the group of IVIG and methylprednisolone pulse therapy had an expressively shorten hospitalization duration as compared with the IVIG alone group “ 41.81 ± 25.37 with the comparison of 52.86 ± 55.81 days, $p = 0.006$ ” (Sabharwal et al., 2015).

The admission per year also divided into three categories such as 2000-2004, 2005-2008 and finally 2009-2013. A month mortality, 180 days of seizure and neurologic results were improved in multiple admission years. Univariate regression analysis also used which include the severity of seizure, admission year, and total numbers of drugs of anti-epileptic and treatment group, every major result and consumed multivariate analysis of regression regarding every major result which further comprises only on those variables important at the $p < 0.1$ univariate analysis level. Accordingly, outputs represented there is no statistical significance while utilizing analysis of multivariate regression for treatment group and admission year (Shorvon and Ferlisi, 2012).

4.0 DISCUSSION:

It is basically a severe challenge to treat children affected with febrile RSE, specifically in a pediatric ICU and when there high morbidity and mortality rates have also been stated. Presently, cumulative

proof has advised that an inflammatory process and immune-mediated mechanism may contribute a major role in subsequent epileptogenesis and this disease (Shorvon and Ferlisi, 2012).

There is a high rate of mortality and morbidity according to RSE in child patients, significantly, in those which have “acute symptomatic etiology” of which most common is encephalitis. According to a meta-analysis regarding RSE in children, the rate of mortality was 20%, and no child carrying “acute symptomatic RSE” reverted to baseline. In this analytical study, the rate of mortality of one month was 10%, which is constant with preceding analysis. Therefore, we also identified that there were good seizures and neurological results for 6 months, according to the combination of methylprednisolone pulse therapy and IVIG combination group, from which two patients were returned to baseline. However, hostile immunotherapy with methylprednisolone pulse therapy and IVIG combination also play a successful role in the handling of febrile RSE (Lin et al., 2018).

5.0 CONCLUSION:

In children, febrile status epilepticus is a major and significant kind of status epilepticus. Those patients which have RSE have also increased rates of morbidity and mortality, accordingly, inflammatory processes and immune-treated mechanisms looked to play a highly significant role in epileptogenesis and disease severity. This reflective analytical study presented that those patients who took a combination of methylprednisolone pulse therapy and IVIG combination were linked with a good seizure and neurological results in six months as compared with those which did not take immunotherapy, similarly, with those who took IVIG alone. However, it is very problematic to generate difference the advantages regarding aggressive immunotherapy from enhancement of serious care administration by years. Additional prospective analytical studies required to confirm these outcomes.

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