INTRAVENTOUS IMMUNOGLOBULIN FOR POST-POLIO SYNDROME: A DOUBLE-BLINDED, PLACEBO CONTROLLED, RANDOMIZED TRIAL

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Post polio conference, Copenhagen,
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BACKGROUND: PATHOGENESIS

HYPOTHESIS

VIRAL

DEGENERATIVE

INFLAMMATORY
INFLAMMATORY PROCESS

Prior poliomyelitis—IVIG treatment reduces proinflammatory cytokine production

Henrik Gonzalez a,b,*, Mohsen Khademi c, Magnus Andersson a,c, Fredrik Piehl c, Erik Wallström a,c, Kristian Borg a,d, Tomas Olsson c

- 16 pts
- IVIG 90g
  - blood and CSF INF-γ mRNA TNF-α
Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial

Henrik Gonzalez, Katharina Sibrant Sunnerhagen, Inger Sjöberg, Georgios Kaponides, Tomas Olsson, Kristian Borg

Summary

Background Survivors of poliomyelitis often develop increased or new symptoms decades after the acute infection, Lancet Neurol 2006; 5: 493-500

European Journal of Neurology 2007, 14: 60–65
doi: 10.1111/j.1468-1331.2006.01552.x

Post-polio syndrome patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study

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SHORT COMMUNICATION

EFFECT OF INTRAVENOUS IMMUNOGLOBULIN IN PATIENTS WITH POST-POLIO SYNDROME – AN UNCONTROLLED PILOT STUDY

Georgios Kaponides, MD\textsuperscript{1}, Henrik Gonzalez, MD\textsuperscript{1}, Tomas Olsson, MD, PhD\textsuperscript{2} and Kristian Borq, MD, PhD\textsuperscript{1}
Two arms double blinded Randomized Controlled Trial (treatment vs placebo)
50 pts IVIG/placebo
IVIG 0.4g/kg for 5 days/placebo saline
1. History of acute poliomyelitis and Post-polio diagnosis according to Halstead’s criteria (Orthopedics 1991; 14: 1209-1217), reconfirmed in 2006 by ENFS - anamnesis and neurological examination (muscle atrophy, depressed reflexes) - electrophysiological examination

2. Exclusion of any other neurological, orthopaedic or medical problems as causes of symptoms - electrophysiological examination - laboratory analysis - (orthopaedic examination) - (imaging)
Diagnosis of postpolio syndrome

1. History of previous established episodes of paralytic polio
2. Partial or fairly complete recovery
3. Period of functional and clinical stability: at least 15 years
4. Sudden or gradual onset of new symptoms and signs of muscle dysfunction:
   - muscle weakness or abnormal muscle fatiguability,
   - generalized fatigue
   - new muscle atrophy
   - muscle or joint pain,
   - loss of muscle function
   - cold intolerance
Lo studio neurofisiologico dovrà dimostrare:

ENG and EMG
- Signs of old neurogenic reorganization due to previous poliovirus infection
- Signs of new lower motor neuron lesions

Electrophysiological examination:

SEPs
- Normal sensory findings: useful to rule out root or nerve trunk pathology
Further investigations:

**Imaging studies:** mainly spinal MRI in order to rule out entrapment or root compression

**Orthopaedic evaluation:** to rule out bone or joint involvement
EXCLUSION CRITERIA

- BMI > 30
- Diabetes Mellitus
- Mild or severe heart disease
- Renal Failure
- Hypertension
- History of thromboembolism
- Oral anticoagulant therapy
- Previous IVIG treatment
- IgA deficiency
- Other autoimmune diseases
- Age > 70yrs
- Other causes of contraindication to therapy
- Other causes able to explain the complained symptoms
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>treated</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of infection mths (mean± SD)</td>
<td>22.7 ±18.5</td>
<td>34.8 ±45.0</td>
</tr>
<tr>
<td>Age of onset of PPS yrs</td>
<td>48.4±6.8</td>
<td>47.9±9.9</td>
</tr>
</tbody>
</table>
1. Selection of patients according to inclusion and exclusion criteria
2. Presentation of the project to the patient which also receives informed consent form
3. Electrophysiological examination:
   - 4 limbs ENG
   - EMG $\rightarrow$ stable muscle (no variations over time)
     $\rightarrow$ healthy muscle (not interested by acute infection)
     $\rightarrow$ worsened muscle (new muscle weakness after a period of clinical stability of at least 15 years)
   - 4 limbs TMS
   - 4 limbs SEP
4. Laboratory workup:
   - Blood count
   - IgA titration
   - Liver and renal function
   - Serology for HIV and haepatitis
### PHASE II

**Patient’s clinical evaluation:**

<table>
<thead>
<tr>
<th>Muscular Strength</th>
<th>MRC Dynamic dinamometer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Fatigue severity scale (FSS)</td>
</tr>
<tr>
<td>Pain</td>
<td>Visual Analogue Scale (VAS) 101 Point Numerical Rating (101-PNR)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>SF-36 (36 item Short-Form)</td>
</tr>
<tr>
<td>Muscle function</td>
<td>6 minutes walking test (6 MWT)</td>
</tr>
</tbody>
</table>
25 PATIENTS
IVIG 0.4 g/Kg/daily for 5 consecutive days

25 CONTROLS
PLACEBO (saline) at the same way

Infusion:
- initial speed: 0.46-0.92 ml/kg/h → 10-20 drops/min
- maximal speed: 1.85 ml/Kg/h → 40 drops/min
### PHASE IV

#### CLINICAL FOLLOW-UP
- MRC and Dynamometer
- FSS
- VAS and 101-PNR
- SF-36
- 6 MWT

#### ELECTROPHYSIOLOGICAL FOLLOW-UP
- 4 limbs ENG
- 3 muscle EMG
- 4 limbs SEP
- 4 limbs TMS

- 2 months
- 4 months
Estimated period of participation of the patient: 6 months

The patient can stop the treatment and leave the study at anytime.
Double blinded study
Randomization codes elaborated with statistical software STATA 9.2 *(HYPERLINK)* by the department of epidemiology and medical statistics, of the University of Verona and delivered to Bussolengo ASL pharmacist
Every patients gets a code which he/she keeps for the duration of the whole study
Pharmacy of Bussolengo Hospital prepares the samples: same bags labelled and screened containing IVIG and saline
• PRIMARY END POINT:
  Improvement of physical component of SF-36 in treated patients versus placebo
• SECONDARY END POINTS:
  – Increase in muscular strength (MRC, Dynamometer)
  – Reduction of fatigue (FSS)
  – Reduction of pain (VAS, 101-PNR)
  – Improvement in physical ability (6 MWT)
Assuming:
- An improvement of at least 4 points in the score of physical component of SF-36 \((Gonzalez \ et \ al. \ 2004; \ Kaponides \ et \ al. \ 2006)\)
- Alfa= 0,05
- Power of 80%
- correlation 0,9 (two measures on the same subject)
- Randomization ratio 1:1

…we need 21 subjects in every arm

Which will be raised to 25 PATIENTS in account of possible dropouts
“INTENTION TO TREAT” analysis
Primary and secondary endpoints:
Comparison of differences in the score of the scale used before and after treatment in the two groups by means of
• T-TEST (in case of gaussian distribution)
• MANN-WHITNEY’s TEST (in case of non gaussian distribution)

If necessary check out for biases (eg, severity of pathology, age):
• COVARIANCE ANALYSIS
  – Dependent variable: difference between values in variables before and after treatment/placebo
  – Indipendent variable: group (treatment/placebo); age; disease severity
Statistical analysis by means of software STATA 9.2
3 RESULTS
PRIMARY ENDPOINTS
SF36- pc

Wilcoxon p=0.02

IVIG
placebo

*
STRATIFIED ANALYSIS

<table>
<thead>
<tr>
<th>Sex</th>
<th>F</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of infection</td>
<td>&lt;15,5</td>
<td>&gt;15,5</td>
</tr>
<tr>
<td>Age of worsening</td>
<td>&lt;50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Time since PPS diagnosis yrs</td>
<td>&lt;7,5</td>
<td>&gt;7,5</td>
</tr>
<tr>
<td>FSS T0</td>
<td>&lt;53,5</td>
<td>&gt;53,5</td>
</tr>
<tr>
<td>VAS T0</td>
<td>&lt;5,5</td>
<td>&gt;5,5</td>
</tr>
<tr>
<td>6 min walking T0</td>
<td>&lt;296,5</td>
<td>&gt;296,5</td>
</tr>
<tr>
<td>SF36-pcT0</td>
<td>&lt;24,9</td>
<td>&gt;24,9</td>
</tr>
</tbody>
</table>
6 min WALKING

Serie1
Serie2
women
IVIG
placebo

* Wilcoxon p=0.012

Sex
women

Wilcoxon p=0.012
FSS

IVIG

placebo

Wilcoxon p=0.008

Age of infection

<15.5

>15.5
FSS

IVIG  Wilcoxon  p=0.012  placebo

Time to treatment
FSS

IVIG

Wilcoxon $p=0.002$

placebo

FSS  T0

*
6 min Walking

IVIG              Wilcoxon p=0.04          placebo

<53.5  <53.5  >53.5

IVIG placebo

*T0

T1

FSS  T0
VAS

IVIG  \[\text{Wilcoxon } p=0.006\]  placebo

VAS T0

\[<5.5\]  \[>5.5\]

T0  T1
FSS

IVIG

placebo

Wilcoxon \( p=0.02 \)

6 min walking
Patients treated with IVIg had significant improvement of SF36-pc

- Women vs men: significant improvement of 6 min walking test
CONCLUSION

• most severe clinical conditions receive the greatest benefit from the treatment
LIMITATIONS and QUESTIONS

• OPTIMAL THERAPY CYCLE
• TREATMENT INTERVALS
• LONG-TERM EFFECTS
• OPTIMAL DOSE
• RESPONDERS AND NONRESPONDERS
• Gonzalez, 2006

• Farbu, 2007

• Kaponides, 2006

IVIg

STRENGTH

PAIN

SF 36