Treatment of Neonatal Sepsis with Intravenous Immune Globulin

The INIS Collaborative Group*


September 29, 2011
Background

- In the year 2000, there were 4 million neonatal deaths worldwide

Background

• Neonatal infection and inflammation are associated with serious complications such as brain damage and disability particularly in preterm infants

• Polyvalent IgG immune globulin may help to prevent or treat infection particularly in preterm infants, who have low serum IgG levels
IgG values at birth ranged from 260 mg/dL to 1440 mg/dL (median 600-700 mg/dL)

Background

• Possible immunomodulating mechanism
  – Enhancement of opsonic activity
  – Complement activation
  – Antibody-dependent cytotoxicity
  – Improvement in neutrophil chemiluminescence
  – Down-regulation of inflammatory cytokines

Background

• 2002 systematic review of 7 trials of adjunctive therapy with IVIG involving 338 newborn infants of any gestational age who had suspected or proven sepsis showed no difference in mortality

• Cochrane Database Syst Rev 2002; 1:CD001090
Background

• 2004 systematic review of 19 trials involving more than 5000 preterm or low-birth weight infants

• Prophylactic use of IVIG reduced the rate of late-onset infection by 3% with no significant reduction in the rates of death and adverse effects

Background

• 2 other systematic reviews suggested that adjunctive therapy with IVIG reduced mortality

• A 1998 review recommended use of IVIG routinely in cases of proven sepsis “a conclusion that many observers might find premature”

Background

- Cochrane 2010 review looking at 10 trials of varying quality on the use of IVIG for suspected or subsequently proven infection in neonates
- Mortality reduced among patients with clinically suspected infection in 7 trials involving 378 infants (RR 0.58; 95%CI 0.38 to 0.89)
- Mortality reduced in pts with subsequently proven infection in 7 trials involving 262 patients (RR 0.55; 95% CI 0.31 to 0.98)

- Cochrane Database Syst Rev 2010;3:CD001239
Background

• Systematic review of 14 randomized, controlled trials of therapy with IVIG in 1450 adults with sepsis suggested a substantial reduction in mortality.

• When meta-analysis restricted to 738 patients in the 4 randomized, controlled trials of larger size or higher quality, the mortality reduction was LOST.

Objective

• No trials of prophylaxis or therapy with IVIG have assessed subsequent disability
• This is a double-blind, randomized, placebo-controlled trial of adjunctive therapy with human nonspecific polyvalent IgG intravenous immunoglobulin in newborn infants who had suspected or proven sepsis and who were receiving antibiotic therapy
Study Design

• In accordance with the protocol for the International Neonatal Immunotherapy Study (INIS)

• Europe, Argentina, Australia, New Zealand

• Study drug purchased with fund from study grants

• Manufacturers had no role in trial design, conduct or analysis
Study Patients

• Inclusion criteria
  – Neonate receiving antibiotics for tx of proven or suspected serious infection with at least one of the following characteristics
    • Birth weight <1500g (3.3 lbs)
    • Evidence of infection in blood culture, csf, or usually sterile body fluid
    • Need for respiratory support through ET tube
Study patients

• Exclusion criteria
  – Previous administration of IVIG
  – Decision by clinical staff that IVIG was either definitely needed or contraindicated
Study patients

- Infants were randomly assigned in a blinded fashion to receive either IVIG or placebo
  - Europe + Argentina: Neonatal staff opened the next sequentially numbered study pack, which was stored in the NICU
  - Australia + New Zealand: hospital pharmacy contacted and next assignment taken from a randomization list
Clinical Management

- IVIG dose was 500mg/kg, administered once and repeated after 48 hours
- Europe + Argentina: IVIG + Placebo made by the Protein Fractionation Centre of the Scottish National Blood Transfusion Service
  - Active drug and placebo were reconstituted by clinical staff by mixing NS with freeze-dried plugs of study product, placebo was 0.2% albumin
- Australia + New Zealand: Pharmacy made up either Intragram P IVIG or placebo was (NS)
Clinical management

• Infused over 4 to 6 hours
• No further IVIG or placebo could be given after administration of the two doses
• Other aspects of management were left to the pediatrician responsible for the infant’s care
Primary Outcome

• Primary outcome:
  – Rate of death or major disability at age 2 years with adjustment for gestational age
Primary Outcome

• Major disability assessed with questionnaires sent to parents and health care professionals
  • Neuromotor function, Seizure, Auditory function, Communication, Visual function, Cognitive function, Other physical disability

<table>
<thead>
<tr>
<th>PQ</th>
<th>Disability (PQ)</th>
<th>HSQ</th>
<th>Disability (HSQ)</th>
<th>Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unable to walk even with help</td>
<td>Major</td>
<td>Has an unsteady walk</td>
<td>Non-major</td>
<td>Major</td>
</tr>
<tr>
<td>Has an unsteady walk but doesn't need help</td>
<td>Non-major</td>
<td>Has an unsteady walk</td>
<td>Non-major</td>
<td>Non-major</td>
</tr>
<tr>
<td>Walks well without help</td>
<td>None</td>
<td>Walks well without help</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Unable to walk without help</td>
<td>Major</td>
<td>No answer</td>
<td>Not known</td>
<td>Major</td>
</tr>
<tr>
<td>No answer</td>
<td>Not known</td>
<td>No answer</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Walks well without help</td>
<td>None</td>
<td>Has an unsteady walk</td>
<td>None</td>
<td>Non-major</td>
</tr>
</tbody>
</table>
Primary Outcome

- Cognitive function assessed on basis of parental reports with the use of the validated PARCA-R (Parent Report of Children’s Abilities-Revised)
  - Score of <31 on a scale 0 to 158 used to identify major cognitive delay
Secondary short-term outcomes

• Rates of death before hospital discharge
• Chronic lung disease (O2 dependency 28 days after birth)
• Major cerebral abnormality
• Relevant positive culture after trial entry (and organism)
• Pneumonia
• Necrotizing enterocolitis
• Length of hospital stay
Secondary long-term outcomes

- At 2 years with adjustment for gestational age
- Rates of death
- Rates of major disability
- Rates of nonmajor disability
  - PARCA parents’ questionnaire
  - questions respiratory function, hearing, vision, hospital admissions, relevant diagnoses and current function in a number of domains, allowing categorization of disability as major or non-major
Statistical Analysis

• Original sample-size estimate based on range of rates for the primary outcome because no reliable data were available

• Intially planned: enrollment of 5000 infants
  – event rates between 15 and 30% for a power of 90% to determine a relative reduction in risk of primary outcome of 14 to 25%

• After meeting of the independent data and safety monitoring committee in 12/2005, data for 2003 infants analyzed
  – steering committee advised that the primary outcome noted to be more frequent than estimated in protocol
  – enrollment of 3500 infants would provide power of 90% to determine a relative risk reduction of 14%
3493 Infants underwent randomization

1759 Were assigned to receive IVIG
  First infusion
    1735 Received complete infusion
    16 Received partial infusion
    8 Did not receive infusion
  Second infusion
    1640 Received complete infusion
    11 Received partial infusion
    58 Did not receive infusion
    49 Died before second infusion
    1 Had missing data

43 Were lost to follow-up
  4 Were adopted
  5 Emigrated
  34 Had missing data

1701 Were included in the follow-up analysis
  15 Were excluded from the analysis because of missing data

1734 Were assigned to receive placebo
  First infusion
    1711 Received complete infusion
    11 Received partial infusion
    10 Did not receive infusion
    2 Had missing data
  Second infusion
    1628 Received complete infusion
    11 Received partial infusion
    62 Did not receive infusion
    31 Died before second infusion
    2 Had missing data

43 Were lost to follow-up
  2 Were adopted
  5 Emigrated
  5 Had consent withdrawn by parent
  31 Had missing data

1677 Were included in the follow-up analysis
  14 Were excluded from the analysis because of missing data

Figure 1. Enrollment and Outcomes.
IVIG denotes intravenous immune globulin.
Infant and maternal characteristics were very similar in both the treatment and the placebo groups.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intravenous Immune Globulin (N=1759)</th>
<th>Placebo (N=1734)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory support through endotracheal tube — no. (%)</td>
<td>1136 (64.6)</td>
<td>1126 (64.9)</td>
</tr>
<tr>
<td>Risk of death — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>304 (17.3)</td>
<td>299 (17.2)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1071 (60.9)</td>
<td>1022 (58.9)</td>
</tr>
<tr>
<td>Other</td>
<td>384 (21.8)</td>
<td>413 (23.8)</td>
</tr>
<tr>
<td>Maternal clinical chorioamnionitis — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with condition</td>
<td>251 (14.3)</td>
<td>277 (16.0)</td>
</tr>
<tr>
<td>Missing data</td>
<td>261 (14.8)</td>
<td>256 (14.8)</td>
</tr>
<tr>
<td>Elevated maternal C-reactive protein, &gt;80 mg/liter — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 (2.2)</td>
<td>47 (2.7)</td>
</tr>
<tr>
<td>Not measured</td>
<td>1129 (64.2)</td>
<td>1116 (64.4)</td>
</tr>
<tr>
<td>Missing data</td>
<td>330 (18.8)</td>
<td>333 (19.2)</td>
</tr>
<tr>
<td>Duration of membrane rupture — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 hr</td>
<td>1007 (57.2)</td>
<td>992 (57.2)</td>
</tr>
<tr>
<td>24–48 hr</td>
<td>57 (3.2)</td>
<td>45 (2.6)</td>
</tr>
<tr>
<td>&gt;48 hr</td>
<td>291 (16.5)</td>
<td>297 (17.1)</td>
</tr>
<tr>
<td>Missing data</td>
<td>404 (23.0)</td>
<td>400 (23.1)</td>
</tr>
<tr>
<td>Source of intravenous immune globulin or placebo — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom, Europe, or Argentina</td>
<td>1062 (60.4)</td>
<td>1033 (59.6)</td>
</tr>
<tr>
<td>Australia or New Zealand</td>
<td>697 (39.6)</td>
<td>701 (40.4)</td>
</tr>
</tbody>
</table>
Results

- 98.3% of infants received the first infusion
- 93.5% received the second infusion
- 2.3% of infants died between the first and second infusion
- 18 infants 0.5% did not receive any infusion
Results

- Of note, this result was unaltered by varying the cutoff point used to define major disability for the cognitive domain.
• Secondary Outcomes
  – No significant differences
  – Including rates of subsequent episodes of sepsis and causative organisms
  – Also no significant difference in rates of cerebral palsey (8.5% of IVIG and 8.3% of placebo)
Subgroup Analysis of Primary Outcome:

No significant difference in any prespecified group

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>IVIG no. of events/total no.</th>
<th>Placebo no. of events/total no.</th>
<th>Relative Risk (99% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500 g</td>
<td>552/1109</td>
<td>558/1279</td>
<td>1.00 (0.86–1.15)</td>
<td>0.14</td>
</tr>
<tr>
<td>≥1500 g</td>
<td>134/392</td>
<td>119/398</td>
<td>1.14 (0.87–1.49)</td>
<td></td>
</tr>
<tr>
<td>Size for gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>186/365</td>
<td>196/387</td>
<td>1.01 (0.84–1.21)</td>
<td>0.37</td>
</tr>
<tr>
<td>≥10th percentile</td>
<td>298/1334</td>
<td>480/1289</td>
<td>1.00 (0.88–1.14)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;26 wk</td>
<td>234/427</td>
<td>197/392</td>
<td>1.09 (0.92–1.30)</td>
<td>0.56</td>
</tr>
<tr>
<td>26–27 wk</td>
<td>164/415</td>
<td>190/442</td>
<td>0.88 (0.71–1.08)</td>
<td></td>
</tr>
<tr>
<td>28–29 wk</td>
<td>105/311</td>
<td>124/305</td>
<td>0.83 (0.63–1.09)</td>
<td></td>
</tr>
<tr>
<td>≥30 wk</td>
<td>183/528</td>
<td>166/538</td>
<td>1.12 (0.90–1.41)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Male</td>
<td>422/964</td>
<td>421/975</td>
<td>1.01 (0.89–1.16)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>264/717</td>
<td>256/702</td>
<td>0.96 (0.82–1.13)</td>
<td></td>
</tr>
<tr>
<td>Maternal chorioamnionitis</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>&lt;30 wk with chorioamnionitis</td>
<td>80/197</td>
<td>95/215</td>
<td>0.93 (0.68–1.24)</td>
<td></td>
</tr>
<tr>
<td>&lt;30 wk without chorioamnionitis</td>
<td>316/777</td>
<td>333/742</td>
<td>0.91 (0.78–1.06)</td>
<td></td>
</tr>
<tr>
<td>≥30 wk</td>
<td>183/528</td>
<td>166/538</td>
<td>1.12 (0.90–1.41)</td>
<td></td>
</tr>
<tr>
<td>Elevated maternal CRP (&gt;80 mg/liter)</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>&lt;30 wk with elevated CRP</td>
<td>13/30</td>
<td>15/39</td>
<td>1.13 (0.53–2.38)</td>
<td></td>
</tr>
<tr>
<td>&lt;30 wk without elevated CRP</td>
<td>77/213</td>
<td>69/189</td>
<td>0.96 (0.68–1.36)</td>
<td></td>
</tr>
<tr>
<td>≥30 wk</td>
<td>183/528</td>
<td>166/538</td>
<td>1.12 (0.90–1.41)</td>
<td></td>
</tr>
<tr>
<td>Membrane rupture</td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>&lt;17 wk with membrane rupture ≥48 hr</td>
<td>104/277</td>
<td>111/283</td>
<td>0.94 (0.71–1.24)</td>
<td></td>
</tr>
<tr>
<td>&lt;17 wk with membrane rupture 24 to &lt;48 hr</td>
<td>14/31</td>
<td>16/35</td>
<td>0.85 (0.57–1.27)</td>
<td></td>
</tr>
<tr>
<td>≥17 wk with membrane rupture ≥48 hr</td>
<td>353/812</td>
<td>346/838</td>
<td>1.00 (0.85–1.16)</td>
<td></td>
</tr>
<tr>
<td>≥17 wk</td>
<td>43/150</td>
<td>44/163</td>
<td>1.06 (0.66–1.70)</td>
<td></td>
</tr>
<tr>
<td>Risk of death</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>High</td>
<td>195/294</td>
<td>173/294</td>
<td>1.13 (0.95–1.33)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>365/1035</td>
<td>367/988</td>
<td>0.95 (0.82–1.11)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>126/372</td>
<td>137/395</td>
<td>0.98 (0.75–1.30)</td>
<td></td>
</tr>
<tr>
<td>Type of Infection</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Early onset</td>
<td>21/45</td>
<td>14/50</td>
<td>1.67 (0.82–3.40)</td>
<td></td>
</tr>
<tr>
<td>Late onset</td>
<td>250/646</td>
<td>237/624</td>
<td>1.02 (0.85–1.22)</td>
<td></td>
</tr>
<tr>
<td>After surgery</td>
<td>13/22</td>
<td>16/27</td>
<td>1.00 (0.54–1.84)</td>
<td></td>
</tr>
<tr>
<td>Source of IVIG or placebo</td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>UK, Europe, or Argentina</td>
<td>464/1023</td>
<td>440/1001</td>
<td>1.03 (0.91–1.17)</td>
<td></td>
</tr>
<tr>
<td>Australia or New Zealand</td>
<td>222/678</td>
<td>237/676</td>
<td>0.91 (0.77–1.14)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Subgroup Analyses of Rates of Death or Major Disability at 2 Years of Age (Primary Outcome).
The P value for the gestational age at birth was calculated by means of the chi-square test for trend. CRP denotes C-reactive protein, IVIG intravenous immune globulin, and UK United Kingdom.
Figure S1: Survival curves for mortality by allocated group

Kaplan-Meier survival estimates

At risk (events):
- IVIG
- Placebo

Time from infusion to death (days)

Proportion alive

Allocation
- IVIG
- Placebo

Legend
Discussion

• Unable to accurately determine the proportion of eligible infants who were recruited to participate in the trial

• Thresholds for study entry varied according to the center and the individual clinician
  – Serious suspected or proven infection, no micro evidence required
Discussion

• Study similar to similar to earlier trials with respect to dose of IVIG used and characteristics of infants at the time of presentation with clinical sepsis
• Compliance with the protocol was very high
• Inclusion criteria were broad
• The prespecified subgroup analysis included larger numbers of neonates than the existing meta-analyses of ALL neonatal data
Discussion

• Important feature of study is assessment of later disability
  – Information about outcome at 2 years was available for 97% of surviving infants

• On basis of established role of IVIG in modifying the course of inflammatory conditions of the CNS in adults, authors hypothesized that the immunomodulatory effects of IVIG might extend to inflammatory injury in the developing brain or lungs
  – No difference in any measure of CNS function, even when restricted to preterm infants (26 to 29 wks gestation)
  – No difference in rates of oxygen dependency at 28 days
Discussion

• In 3 earlier trials, IVIG enriched with IgM was given
  – Although these trials were small, not randomized, placebo-controlled, or blinded
Conclusion

• IVIG was not associated with significant differences in the risk of major complications or other adverse outcomes in neonates with suspected or proven sepsis