Large and simple randomized clinical trial with low dose aspirin for prevention of low birth weight and perinatal mortality in Brazil

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Low dose aspirin in pregnancy prevents pre-eclampsia (1) (2). But prevents fetal deaths? To answer this question in the developed countries is necessary approximately 10,000 patients to be randomized, due to the low incidence rate of perinatal mortality.

In Brazil we verified in a prospective cohort study of chronically hypertensive pregnant women a perinatal mortality rate of 13.0% (3). This information brings us besides the importance of the problem, the possibility to test the hypothesis very quickly whether aspirin may reduce fetal deaths.

For more than a decade Peto et cols. (4) has emphasized the needs of large and simple randomized clinical trials to test effectiveness of any proposed treatments, looking at important outcomes, simple enough to allow large sample size.

So we designed a large randomized clinical trial making it simple to be developed in São Paulo - Brazil. This clinical trial is ECPPA - Collaborative study for prevention of pre-eclampsia with low dose aspirin. In this report we present the experience up the randomization of the first five hundreds patients.

METHODS

We invited by mail 800 obstetricians of different cities of the state of São Paulo - Brazil, to
participate of a collaborative study of low dose aspirin in pregnancy.
Four hundred obstetricians plus eleven schools of medicine decided to join ECPPA.
Each doctor and school received copies of the study proposal and codified treatment packages.
A 24 hours randomization system by telephone and Beep was assembled at Escola Paulista of Medicina in São Paulo, the state capital.

INCLUSION CRITERIA

1) Doctors criteria - the patient's doctor decides if the patient is suitable to be included or not.
2) Uncertainly criteria - if certain that aspirin is useful treat patient and do not randomize. If is sure that aspirin is not indicated, do not include. If uncertain about aspirin effect, randomize.

Suggestions in the protocol as example of cases to be considered for randomization:
 a) Chronic hypertension
 b) Primigravidas
 c) Nephropathy
 d) Intrauterine grow retardation
 e) Unfavorable obstetric past

EXCLUSION CRITERIA

a) Doctors criteria
b) Informed consent not obtained
c) Gastric ulcer
d) Allergy to aspirin
e) Placental bleeding
f) Coagulopathy

DRUG ADMINISTRATION

Doctors have the codified treatment packages in their offices. These are codified boxes with aspirin tablets of 60 mg or placebo displayed in calendar packs. When there is a case to be included the collaborator calls the randomization center and receive the number of the box, to be delivered to the patient.

The list of random numbers were obtained of a computer program.

SAMPLE SIZE CALCULATION

Assuming a perinatal mortality rate of 10% able to be prevented by low dose aspirin, fixing a type I error of 0.05% and type II of 10%. We calculated that with 578 cases in each group there will be 90% chance of detecting a 50% reductions in the perinatal mortality rate with 95% confidence internal. However the aim will be obtain 4000 cases to be able of detecting important reduction as 20% in perinatal mortality.
The outcomes to be followed after the randomization are:

1) Proteinuric preeclampsia
2) Blood pressure
3) Live births, still births, neodeaths
4) Birthweight
5) Mother transfusion and bleeding
6) I.U.G.R.
7) Rate of cesarian sections

Stimulations for collaboration
1) Collaborators receive the ECPPAs Newsletter every two months. It contains information about hypertension in pregnancy and about the trial development.
2) Meetings for collaborators. Experts give talks about hypertension in pregnancy. We did had 5 up to date, being four with Doctor Collins of Oxford University and one with Doctor Michael de Swiet from University of London. Brazilian experts participate as well.
3) Letters and telephone calls.
4) All collaborators will be considered authors of the resulting paper.

Prevention of drop outs
During randomization is obtained the telephone numbers of the patients home, husband or patient work place, and a relative or best friend.

Prevention of contamination
Patients are advised to not take aspirin for pain relieve. Tylenol is recomended in this case.

Evaluation of compliance
Ten per cent of patients choosed by chance and or their husbands are interviwed about the tablets intake.

Preliminary results
The figure I shows the montly randomization rate.

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ECPPA'S RANDOMIZATION RATE

![Graph showing montly randomization rate]
Table I shows the types of patients selected by the doctors for inclusion in this trial. Table II shows the compliance of 50 patients randomized of the first 5 hundred patients. Table III shows the outcomes of the first 3 hundred deliveries obtained up to now.

**Table I**

<table>
<thead>
<tr>
<th>OUTCOMES BEFORE RANDOMIZATION</th>
<th>NUMBER OF PATIENTS</th>
<th>PERCENTUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.U.G.R.</td>
<td>44</td>
<td>9,00 %</td>
</tr>
<tr>
<td>SYSTOLIC BLOOD PRESSURE &gt; 14</td>
<td>76</td>
<td>15,54 %</td>
</tr>
<tr>
<td>DIASTOLIC BLOOD PRESSURE &gt; 9</td>
<td>68</td>
<td>13,91 %</td>
</tr>
<tr>
<td>CASES WITH FETAL LOSSES &gt; 24 W</td>
<td>05</td>
<td>1,02 %</td>
</tr>
<tr>
<td>NUMBER OF GESTATIONS &gt; 24 W</td>
<td>78</td>
<td>15,95 %</td>
</tr>
<tr>
<td>PREVIOUS H.B.P.</td>
<td>231</td>
<td>47,24 %</td>
</tr>
<tr>
<td>DIABETES</td>
<td>33</td>
<td>6,75 %</td>
</tr>
</tbody>
</table>

**Table II**

<table>
<thead>
<tr>
<th>ESTIMATED COMPLIANCE</th>
<th>PERCENTAGE OF TIME IN WHICH TABLETS WERE REPORTED TO HAVE BEEN TAKEN</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 50 %</td>
<td>1</td>
<td>2,0</td>
</tr>
<tr>
<td></td>
<td>50-75 %</td>
<td>4</td>
<td>9,5</td>
</tr>
<tr>
<td></td>
<td>&gt; 75 %</td>
<td>37</td>
<td>88,0</td>
</tr>
</tbody>
</table>

**Table III**

<table>
<thead>
<tr>
<th>BABIES DATA</th>
<th>NUMBER OF PATIENTS</th>
<th>PERCENTUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVE BIRTHS</td>
<td>200</td>
<td>91,32 %</td>
</tr>
<tr>
<td>STILL BIRTHS</td>
<td>15</td>
<td>6,85 %</td>
</tr>
<tr>
<td>NEODEATHS</td>
<td>4</td>
<td>1,83 %</td>
</tr>
<tr>
<td>TOTAL OD BIRTHS</td>
<td>219</td>
<td></td>
</tr>
</tbody>
</table>

* WEIGHT >=2.500 g  
* AVAILABLE  
* WEIGHT >= 1.500 g < 2.500 g  
* WEIGHT < 1.500 g
Considered this is a double blinded randomized clinical trial we are not still allowed to break the codes to compare placebo group with aspirin treatment group.

The first interim analysis will be performed after the first 4 hundred deliveries.

COMMENT

Nowadays there is no doubt that large trials are needed to answer important questions about therapeutics. The conclusions obtained from small trials are not able to detect improvements of 20 or 30%. In the other hand small trials may improve the probability in incorrect conclusions, obtained only by chance.

The more important outcome in the majority of clinical trials is survival. In this study we put these things all together in a place where the perinatal mortality is high, trying to answer if aspirin can decrease fetal deaths.

These preliminary results have 82% power to detect a 50% reduction in the perinatal mortality rate but we are interested to verify if it is possible to detect smaller effect like a 20% reduction.

So we intend to keep going for more two years, to try to reach a minimum of 2000 cases and maximum of 4000.

The data related from the deliveries can be obtained from the doctors, or from a patients relatives by telephone calls. Provide that we are mostly interested in birth weight and perinatal mortality.

During this first twelve months of experience we consider possible to develop large and simple clinical trial in an undeveloped country.

REFERENCES