LOW DOSE ASPIRIN IN PREVENTION OF PRE-ECCLAMPSIA AND IUGR A FOGSI MULTICENTRIC STUDY

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SUMMARY

A multicentric study was carried out by F.O.G.S.I. Clinical Research Committee in 9 institutions to assess the effectiveness of low dose aspirin for prevention and treatment for preeclampsia and IUGR.

A total of 1216 patients received low dose aspirin or placebo. The antenatal, intrapartum and perinatal records were maintained. The patients were divided into three groups - therapeutic, prophylactic and primigravida. There was significant reduction in eclampsia in patients who took low dose aspirin in the therapeutic group. Induction of labour was carried out when there were possibilities of increasing severity of preeclampsia, placental insufficiency and fetal distress. In both the therapeutic as well as prophylactic groups there was significant reduction in the need for induction in patients on low dose aspirin. In the therapeutic group of patients, the IUGR and preterm labour were significantly reduced in patients who were on aspirin. However, in prophylactic group aspirin did not show significant effect and in primigravida even less so. Initiation of treatment in early second trimester, proper selection, good counselling as well as compliance and good followup are most essential to ensure effectiveness of the therapy.

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INTRODUCTION

The encouraging preliminary results of

antiplatelet therapy for prevention and treatment of preeclampsia and IUGR were followed by many clinical trials where low dose aspirin was used in dosages varying from 60 to 150 mg/day. The FOGSI Clinical Research Committee conducted a multicentric study in nine institutions between 1991 to 1994 to assess the effectiveness of low dose aspirin for prevention and treatment of pre-eclampsia and IUGR. This paper presents the results of 1216 patient where aspirin or placebo was used for patients with early pre-eclampsia or IUGR as well as for patients who were thought to be at greater than average risk of developing preeclampsia or IUGR.

The rationale of utilization of low dose aspirin in pre-eclampsia is well accepted. Structural and occlusive changes in the spiral arteries and underperfusion of the uteroplacental circulation lead to fetal growth failure. By blocking the synthesis of platelet aggregating and vasoconstricting agent thromboxane; and rectifying the imbalance between thromboxane and prostacyclin, a vasodialator, these pathological changes could be ameliorated by low dose aspirin. As pre-eclampsia is one of the most common complications of pregnancy which affects both the fetus and the mother, prophylactic treatment to prevent severe hypertension, eclampsia, prematurity, IUGR as well as neonatal death is certainly warranted.

MATERIALS AND METHODS

A multicentric, randomized, placebo controlled study was carried out in 9 teaching institutions. Antiplatelet therapy in the form of 100 mg of aspirin or a similar looking placebo tablet was given to patients with early development of hypertension or IUGR in the current pregnancy (therapeutic group). The second group was of patients who were thought to be at risk of developing pre-eclampsia or IUGR because of the previous obstetric history, medical history or significant family history (prophylactic group). The third group was that of primigravidae as PIH is known to affect primigravidae more often. The treatment was initiated between 14 and 32 weeks of gestation. A detailed clinical history and obstetric history was noted and a thorough clinical examination as well as routine laboratory investigations were carried out. Platelet count, serum creatinine, serum uric acid and liver function tests were repeated as and when necessary. Serial sonography and doppler blood flow studies were possible only in few cases. Cases with increased risk of bleeding, e.g. peptic ulcer, bleeding disorders and cases with history of asthma or allergy to aspirin as well as patients likely to deliver in near future were excluded. Patients were followed up in the antenatal clinic and admitted when necessary. Obstetric examination, weight gain, blood pressure, fetal growth and requirement of anti-hypertensive drugs during pregnancy and labour were noted. The duration of pregnancy at the time of delivery, the mode of delivery and maternal complications such as eclampsia were noted. The information on fetal maturity, fetal distress and neonatal asphyxia as well as neonatal weight was also recorded.

RESULTS

Of 1216 patients, 655 (53.87%) were given aspirin and 561 (46.13%) were given placebo treatment. The therapeutic group had 101 patients (8.3%) with early

pre-eclampsia or IUGR. 44% of the cases were in the prophylactic group and 47.7% were primigravidae. Unfortunately the follow up and compliance were not satisfactory and we are able to present the results of only 50% of the originally enrolled cases. The results in the therapeutic group were most significant. It has been observed that the effectiveness of prophylactic low dose aspirin is maximum if started in early second trimester. Unfortunately, most of our patients registered for their antenatal care rather late and we could start the therapy of 20 weeks only in 3.8% of women in aspirin

Table I
INCIDENCE OF ECLAMPSIA

Group	Therapy	Incidence (%)	p value
Therapeutic	Aspirin	3.5	<0.005
	Placebo	4.9	
Prophylactic	Aspirin	3.2	<0.005
	Placebo	5.4	
Primi	Aspirin	1.6	NS
	Placebo	2.4	

Table II
NEED FOR INDUCTION OF LABOUR AND MODE OF DELIVERY

Group	Outcome	Aspirin (%)	Placebo (%)	Value
Therapeutic	Induction	15.38	38.784	<0.05
	Spontaneous	67.31	44.89	<0.05
	LSCS	11.54	12.24	NS
	Vacuum, Forceps	5.77	4.08	NS
Prophylactic	Induction	2.44	7.26	<0.01
	Spontaneous	86.41	81.85	<0.05
	LSCS	9.76	9.68	NS
	Vacuum, Forceps	1.39	1.21	NS
Primi	Induction	7.91	9.85	<0.1
	Spontaneous	79.75	75	<0.5
	LSCS	6.96	9.09	<0.1
	Vacuum, Forceps	5.38	6.06	NS

group and in 3.3% of those in placebo group.

A significant result of this study was the reduced incidence of eclampsia in both therapeutic as well as prophylactic group. In the therapeutic group, the incidence of eclampsia was 3.5% and 4.9% in the aspirin and placebo groups respectively. In the prophylactic group 3.2% of women on aspirin and 5.4% of women on placebo developed eclampsia. However, in the primigravidae the incidence was 1.6% and 2.4% in the aspirin and placebo groups which was statistically not significant (Table I). As eclampsia is responsible for considerable maternal and perinatal morbidity and mortality, prevention of this complication is certainly important. There was no significant difference in the incidence of severe hypertension during pregnancy and labour in all the three groups.

Induction of labour was carried out in patients developing maternal or fetal problems such as increasing severity of pre-eclampsia and placental insufficiency with the idea to prevent maternal and perinatal complications. The incidence of induction of labour in the therapeutic group was 15.38% in the patients on aspirin and 38.78% in the patients on placebo. In the prophylactic group, the induction of labour was resorted to in 2.44% of patients on aspirin and 7.26% in placebo group. In the primigravidae, the induction was carried out in 7.91% and 9.89% in aspirin and placebo groups respectively. 67.31% of patients on aspirin and 44.89% of patients on placebo in the therapeutic group had spontaneous vaginal deliveries. However, it should be noted that there was no significant difference in the rate of caesarean section, which was 11.54% and 12.24% in aspirin and placebo groups respectively (Table II).

The gestation age at delivery, the incidence of IUGR and the incidence of preterm delivery were significantly influenced by aspirin in the therapeutic group. 71.15% in the aspirin group and

Table III
GESTATIONAL AGE AT DELIVERY

Group	Outcome	Aspirin (%)	Placebo (%)	Value
Therapeutic	FTND	71.15	53.06	<0.05
	IUGR	25	32.65	<0.01
	Preterm	3.85	14.29	<0.05
Prophylactic	FTND	78.75	86.69	NS
	IUGR	7.67	5.24	NS
	Preterm	13.59	8.06	NS
Primi	FTND	81.96	80.3	NS
	IUGR	11.08	10.61	NS
	Preterm	6.96	0.09	NS

53.06% in the placebo group had full term normal deliveries. The incidence of IUGR was 25% and 32.65% and preterm delivery was in 3.85% and 14.29% in the aspirin and placebo groups respectively (Table III). 94.23% of women on aspirin had livebirths compared to 89.8% of women on placebo in the therapeutic group (Table IV). The mean birth weight was 2438.46 gms and 2263.67 gms in the aspirin and placebo groups respectively (Table V). There was no significant difference in the average duration of labour, Apgar score, retroplacental clots and placental infarcts. The estimated blood loss was also similar in both the groups. No case of congenital abnormality in the newborn was reported.

Table IV
OUTCOME OF LABOUR

Group	Outcome	Aspirin (%)	Placebo (%)	Value
Therapeutic	Live Born	94.23	89.8	< 0.1
	Stillbirth	1.27	4.08	NS
	Neonatal Death	Nil	6.12	< 0.05
Prophylactic	Live Born	96.86	98.79	NS
	Stillbirth	1.74	0.81	NS
	Neonatal Death	1.39	0.40	NS
Primi	Live Born	98.73	96.21	NS
	Stillbirth	1.27	3.03	< 0.1
	Neonatal Death	Nil	0.76	NS

Table V
EFFECT ON BABY WEIGHT

Group	Outcome	Average Wt (gm)	Std. Dev.
Therapeutic	Aspirin	2438.46	550.04
	Placebo	2263.67	552.92
Prophylactic	Aspirin	2660.00	472.97
	Placebo	2622.54	539.04
Primi	Aspirin	2552.5	450
	Placebo	2544.1	445

DISCUSSION

Although this multicentric placebo controlled study did not show very significant effect of prophylactic low dose aspirin in reduction of pre-eclampsia and IUGR, it certainly showed a reduction of perinatal and maternal complications in cases who already had early onset of pre-eclampsia and IUGR. In the therapeutic group the need for induction of labour was less than half and the incidence of preterm delivery was 1/4th in patients who were on aspirin group compared to patients on placebo. Besides, the incidence of eclampsia, a dreaded complication of pre-eclampsia was significantly less in women on low dose aspirin. A meticulous history taking, blood pressure recording and close obstetric monitoring are necessary for proper selection and successful treatment. Chesley and Cooper (1986) have demonstrated a family pattern in pre-eclampsia suggesting an autosomal single recessive trait. Pre-eclampsia can be expected to occur in about 38% of the sisters and 20% of daughters of those who had suffered from this problem. Although angiotensin sensitivity test and doppler blood flow studies are scientific way of selection, it is important to establish proper clinical criteria specially in developing, countries with limited resources. A meticulous blood pressure recording is one of the most important factors. It is necessary to note both the systolic and diastolic pressures and calculate the mean arterial pressure { (Systolic +[2* Diastolic]) /3 }. The rise of mean arterial pressure to 90mm or more increase the chance of pre-eclampsia, IUGR and stillbirth. For patients who have registered in first trimester, it is necessary to note a drop of blood pressure in second trimester. Ansence of this phenomena also indicates a higher possibility of pre-eclampsia. Sibai and Caritis et al consider even baseline systolic blood pressure greater than 120 mm Hg as a significant indication for low dose aspirin. The roll over test has been evaluated by many workers. Although a positive roll over test indicates increased risk of pre-eclampsia, the positive predictive value varies tremendously (40-90%) in various studies.

Microalbuminuria and calcium / creatinine ratio helps to prognosticate pre-eclampsia and the cut off points are 11 microgm /ml or more albuminuria and a ratio of less than 0.004 calcium / creatinine.

Personal involvement and care with good counselling improves patient's compliance and follow up. It was unfortunate that there were two resident medical officers strikes during this study for very long periods and a large number of patients could not be followed up to note the obstetric outcome. Investigators who were deeply involved had better selection, closer monitoring and more favourable results.

Mukherjee (personal communication) Rai and Chakarborty (1993) (100 patients), Bhardwaj (1995) (131 patients), Das & Agarwal (1993) (84 patients) have carried out prospective comparative studies and indicated significant benefit of low dose aspirin. Thomas et al (1991) carried out a meta analysis of low dose aspirin for prevention of pregnancy induced hypertensive disease. Among 394 subjects from six trials, the relative risk (RR) of PIH among women who took aspirin was 0.35. Aspirin reduced the risk of severe low birth weight among newborns by 44%. Schiff et al (1989) studied 291 pregnancies and noted that the pro-

portion of women who developed PIH was significantly lower and the overall perinatal outcome improved in the aspirin group. Kilby et al (1994) have presented the overview of available data from randomized controlled trials from 1977 and 1991. The meta analysis of these prospective longitudinal studies have demonstrated a significant effect of low dose aspirin on perinatal mortality and the incidence of proteinuric pregnancy hypertension.

One of the largest collaborative studies (CLASP - Collaborative Low-dose Aspirin Study in Pregnancy) (1994) had 213 centres who recruited 9364 pregnant women.

The use of aspirin was associated with a reduction of only 12% in the incidence of proteinuric pre-eclampsia, which was not significant. There was no significant effect on the incidence of IUGR or of stillbirth and neonatal death. However, aspirin significantly reduced the likelihood of preterm delivery. Their findings do not support routine prophylactic or therapeutic administration of antiplatelet therapy in pregnancy, but justify its use in women judged to be specially liable to early onset of pre-eclampsia severe enough to need preterm delivery. It is also necessary to note that Parazzini (1993), did not find any difference in the two groups, aspirin and placebo, in terms of frequency of abortions, stillbirths, premature births, perinatal mortality, low birth weight of frequency of PIH in their meta analysis form several clinical trials carried out to judge the efficacy of low dose aspirin in women at moderate risk of PIH or IUGR. Our FLASP trial, CLASP (1986) trial as well as the Thomas (1991) analysis showed no significant maternal or neonatal adverse effects resulting from low dose aspirin.

The use of low dose aspirin in primigravidae is controversial. Wallenburg et al (1986) carried out a prospective double blind placebo controlled study and screened 207 apparently normal primis at 28 weeks of gestation by presser sensitivity to infused Angiotensin II. 46 women who were deemed to be high risk were randomized to receive 60 mg of aspirin or placebo. He even assessed patient's compliance by the determination of thrombin induced production of malanoaldehyde by platelets. The study demonstrated significantly reduced incidence of PIH in the treatment group. McParland et al (1990) measured the pulsatility index in the uteroplacental circulation in 1226 primigravidae and carried out a randomised study of 75mg of Aspirin or placebo. In pregnancies with increased resistance index, aspirin significantly reduced proteinuric PIH. Hauth & Goubas (1993) also demonstrated a reduction of pre-eclampsia with 60mg of aspirin given from 24 weeks of gestation. However, Sibai and Caritis (1993) did not find the effect of aspirin significant in unselected healthy nulliparas. Our study also indicated the same. The selection criteria in primigravidae therefore have to be very vigilant.

Aspirin has been shown to prevent thrombotic occlusion of arteriovenous shunts and coronary artery bypass grafts and reduce deaths and reinfarction in unstable angina and cerebral ischaemic attacks. The same logic very much applies to using low dose aspirin to prevent pathological changes of pre-eclampsia and even IUGR where no definite etiologic factor is identified. Changes in the coagulation system with consumption of Factor VIII, reduced circulating platelets, increase in the level of fibrin

degradation products, are documented in pre-eclampsia. The occlusive changes in spiral arterioles cause placental ischaemia, pre-eclampsia, and IUGR which may or may not be associated with pre-eclampsia. Elevated endothelin levels as a result of deported trophoblasts could explain the multi organ involvement in the pre-eclampsia. Aspirin, an anticoagulant or antiplatelet agent when used in low dose inhibits the enzyme cyclo-oxygenase in platelets and blocks and synthesis of platelet aggregating agent thromboxane A2. Patrignani et al (1982) found that doses ranging from 60 mg to 100 mg exerted a linear inhibition of platelet thromboxane with a ceiling effect at 100 mg of aspirin. This dosage therefore gives adequate inhibition of platelet aggregation and higher doses are not necessary. It is necessary to realise that low dose aspirin may not show significant benefit in all the patients as platelet activation represents only a part of the complex pathogenesis of pre-eclampsia. Our FOGSI low dose aspirin study has shown definite benefit in the therapeutic group where the incidence of preterm delivery, low birth weight and the need for induction of labour is reduced with the use of low dose aspiring. Besides maternal morbidity due to eclampsia is also reduced. The benefit is less evident in the prophylactic group and not evident in the primigravidae. Meticulous selection of cases is most essential to see the benefits of low dose aspirin.

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