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Role of 75 mg Versus 150 mg Aspirin in Prevention of Pre-Eclampsia in Women with Previous History of Pre-Eclampsia

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Abstract

Objective: The objective of the study was to study the effect of 75 mg and 150 mg aspirin in prevention of pre-eclampsia in women with previous history of pre-eclampsia.

Method: This prospective interventional study was carried out in the Department of Obstetrics and Gynecology, Pt. B.D. Sharma PGIMS, Rohtak from 2019-2020. Women with previous history of pre-eclampsia who presented at period of gestation less than 16 weeks were included in the study. The patients were divided in two groups, Group-I: 50 patients who received aspirin, 75 mg daily and Group-II: 50 patients who received aspirin, 150 mg daily.

Results: Group I (75 mg of aspirin) and Group II (150 mg of Aspirin) were comparable with respect to age, education and socio-economic status. The mean gestational age of delivery was also comparable. Overall Incidence of pre-eclampsia in present study was 14%. Pre-eclampsia occurred in 8 (16%) women in group-I and 6 (12%) women in group-II. The difference was found to be statistically insignificant. Perinatal complications like low birth weight, preterm delivery, NICU transfer, respiratory distress syndrome and fetal growth restriction were not significantly different in both the groups.

Conclusion: There is no correlation between 75 mg versus 150 mg dose of aspirin and the incidence of pre-eclampsia in women with previous history of pre-eclampsia. Also, 150 mg aspirin had no statistically significant effect on the incidence of secondary outcome (Abruptio placenta, any maternal morbidity, fetal outcome intrauterine growth restriction, intrauterine death, NICU admission, NICU stay and perinatal death) in comparison to 75 mg aspirin.

Keywords: Low dose aspirin; Prevention of preeclampsia.

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INTRODUCTION

Hypertensive disorders are the most common medical complication occurring in 12-22% of all pregnancies and it is directly responsible for 17.6% of maternal deaths in the United States and 24% of all maternal deaths in India.[1,2] Hypertensive disorders during pregnancy occur in women with pre-existing primary or secondary chronic hypertension and in women who develop

new onset hypertension in the second half of pregnancy.[3] Pre-eclampsia refers to the new onset of hypertension (systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg) and proteinuria (>0.3gm protein in 24 hour urine) after 20 weeks of gestation in a previously normotensive woman.[4] Although the exact aetiology of pre-eclampsia is still a mystery, several factors such as obesity, diabetes mellitus, calcium deficiency, advanced maternal age, oxidative stress, placental ischemia, genetics and immune maladaptation have been implicated.[5] Aspirin (acetylsalicylic acid) is a non steroidal anti inflammatory drug (NSAID) that works primarily through its inhibition of two cyclooxygenase isoenzymes (COX-1 and COX-2), which are necessary for prostaglandin biosynthesis. The COX-1 isoform is present in the vascular endothelium and regulates the production of prostacyclin and thromboxane A2, prostaglandins with opposing regulatory effects on vascular homeostasis and platelet function. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, whereas thromboxane A2 (TXA2) is a potent vasoconstrictor and promotes platelet aggregation. The COX-2 isoform is inducible and expressed almost exclusively following exposure to cytokines or other inflammatory mediators. The effect of aspirin on COX-dependent prostaglandin synthesis is dose dependent. At lower dosages (60–150 mg/day) aspirin irreversibly acetylates COX-1, resulting in decreased platelet synthesis of TXA2 without affecting vascular wall production of prostacyclin. At higher doses, aspirin inhibits both COX-1 and COX-2, effectively blocking all prostagland in production.[6,7] World Health Organization recommends that low-dose aspirin (75 mg/day) should be initiated before 20 weeks of gestation for women at high risk of pre-eclampsia; e.g. women with a history of pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, and multiple gestations.[8] The National Institute of Health and Care Excellence published a quality statement, Antenatal Assessment of Pre-eclampsia Risk, in July 2013 that prescribed low-dose aspirin (75 mg/day) to pregnant women at increased risk of pre-eclampsia at the first prenatal visit, to be taken daily from 12 weeks of gestation until birth.[9] The degree of risk of pre-eclampsia was based on the presence of one or more high-risk factors (hypertensive disease in previous pregnancy, chronic kidney disease autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension) or more than one moderate risk factor (first pregnancy, maternal age of 40 years or older, a body mass index greater than 35, family history of pre-eclampsia, and multiple pregnancy).[10,11]

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine support the United States Preventive Services Task Force (USPSTF) guideline criteria for prevention of pre-eclampsia recommended low dose aspirin (81 mg/day) prophylaxis in women at high risk of pre-eclampsia and should be initiated between 12 weeks and 28 weeks of gestation (preferably before 16 weeks) and continued daily until delivery. Women who were receiving medically-indicated low-dose aspirin for other established medical indications before 12–28 weeks may continue with low-dose aspirin treatment.

There is a scarcity of literature about various low doses of aspirin to be used in patients with previous history of pre-eclampsia for prevention of pre-eclampsia. Hence, the present study was planned to see the role of 75 mg vs. 150 mg aspirin in prevention of pre-eclampsia in women with previous history of pre-eclampsia.

METHODS

This prospective interventional study was carried out in the Department of Obstetrics and Gynecology, Pt. B.D. Sharma PGIMS, Rohtak from 2019-2020. Women with previous history of pre-eclampsia who presented at period of gestation less than 16 weeks were included in the study. The patients were divided in two groups, Group-I: 50 patients who received aspirin, 75 mg daily and Group-II: 50 patients who received aspirin, 150 mg daily. In both groups, women who presented in first trimester, aspirin was started from 12 weeks of gestation and in women who presented after first trimesteraspirin was start at period of gestation <16 weeks but not later than 16 weeks. Patients with Diabetes mellitus, chronic hypertension, multiple fetus, chronic kidney disease and auto-immune disease were excluded from the study. Pre-structured patient proforma was used for data collection. The quantitative variables in both groups were expressed as mean ± SD and compared by using unpaired t-test. The qualitative variables were expressed as frequencies/percentages and compared by using Chi-square test. A p-value <0.05 was considered statistically significant. Statistical Package for Social sciences (SPSS) version 21.0 was used for statistical analysis.

RESULTS

It was observed in our study that both the groups were comparable based on demographic profile, with majority of women of age group between 21 to 25 years, graduate and above educated, socio economically mostly were in upper lower class. In both the groups, the women were mostly Gravida 2. The enrolled women were mostly between 12 to 16 weeks gestation in both the groups.

Majority of the women, 38 (76%) in group I and 37 (74%) in group II had delivery at 37-40 weeks. Only 6 (12%) women in group I and 5 (10%) in group II had preterm delivery. Mean gestational age in group I was 38.12±1.47 weeks a range of 32-41 weeks and in group II, it was 38.26±1.62 weeks with a range of 32-41 weeks. On statistical analysis, the difference among both the groups found to be comparable and thus statistically insignificant (p >0.05). Both the groups had insignificant difference in spontaneous and induced labour.

A total of 38 (76%) women in group I and 42 (84%) in group II delivered vaginally. Cesarean section was carried out in 12 (24%) women of group I and 8 (16%) of group II. On statistical analysis, the difference among both the groups found to be comparable and thus statistically insignificant (p >0.05 NS). Fetal distress was the most common indication for caesarean section in both the groups.

Table 1: Maternal Complications

Complications	Group 1 (n=50)	Group 2 (n=50)	Statistical Analysis
Pre-Eclampsia	8 (16%)	6 (12%)	p=0.564 (>0.05 NS)
Abruptio placentae	2 (4%)	1 (2%)	p=0.557 (>0.05 NS)
Preterm labour	6 (12%)	5 (10%)	p=0.749 (>0.05 NS)
PPH	2 (4%)	1 (2%)	p=0.557 (>0.05 NS)
HELLP syndrome	1 (2%)	1 (2%)	p=1 (>0.05 NS)
Eclampsia	1 (2%)	–	p=0.314 (>0.05 NS)
Renal complications	–	–	–
DIC	–	–	–
Intracranial hemorrhage	–	–	–
Mortality	–	–	–
Transfer to RICU/ICU	1 (2%)	–	p=0.314 (>0.05 NS)
Indications for RICU/ICU	1 (2%) Eclampsia	–	p=0.314 (>0.05 NS)

Table 1 shows various type of complications which occurred during the study period in both the groups. In the present study, pre-eclampsia occurred in 8 (16%) women in group I and 6 (12%) women in group II followed by preterm labour i.e. 6 (12%) and 5 (10%), in group I and II, respectively. Abruptio placentae was found in 2 (4%) and 1 (2%) woman of in group I and II, respectively. Postpartum hemorrhage was seen in 2 (4%) and 1 (2%) women of group I and II, respectively. On statistical analysis, the difference among both the groups found to be comparable (p >0.05).

Table 2: Distribution of patients according to period of gestation of onset of pre-eclampsia.

Onset of pre-eclampsia	Group I (n=50) n (%)	Group II (n=50) n (%)	Statistical Analysis
Term	5 (10%)	4 (8%)	
Pre Term	3 (6%)	2 (4%)	p=0.872 (>0.05 NS)
Total	8 (16%)	6 (12%)	

Table 2 depicts distribution of patients according to period of gestation when pre-eclampsia occurred. A total of 8 women in group I and 6 women in group II had pre-eclampsia. Out of 8 cases of pre-eclampsia in group 1, 3 (6%) women had pre-eclampsia before term. Similarly, out of 6 cases in group II, 2(4%) had pre-eclampsia before term. On statistical analysis, the difference among both the groups found to be comparable and thus statistically insignificant (p >0.05).

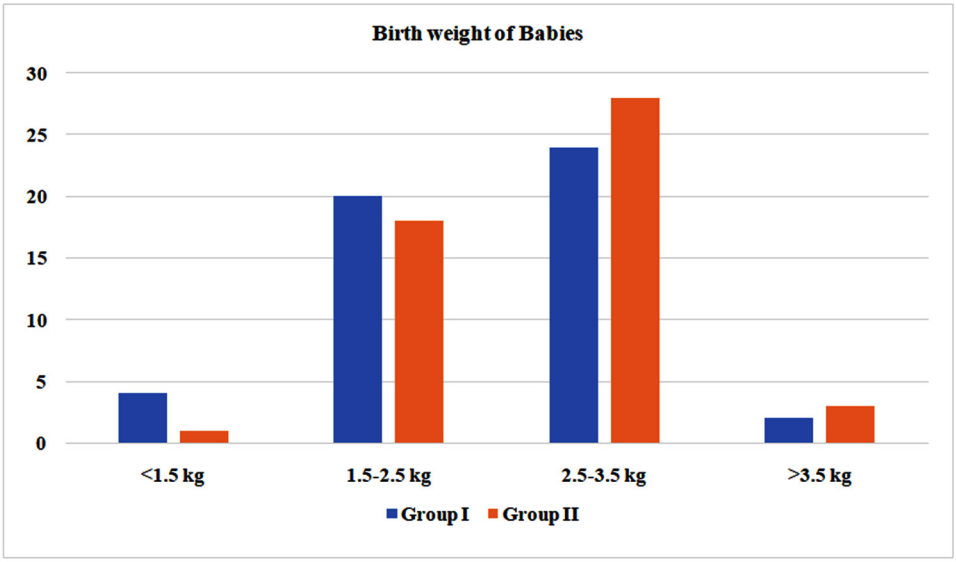

Fig. 1: Comparison of birth weight of babies of Group I and II

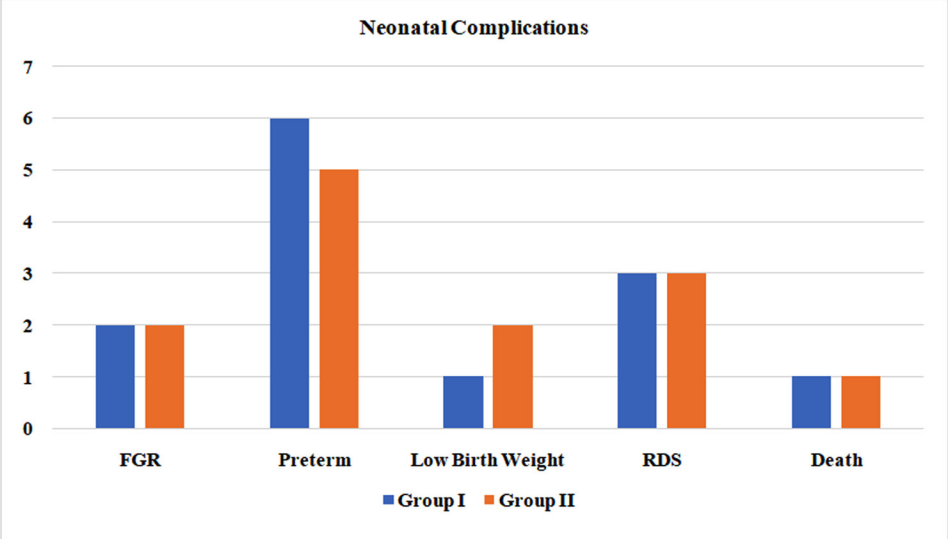

Fig. 2: Neonatal complications in babies of Group I and II

Fig. 1 and 2 show the perinatal outcomes in both the groups, there was no statistical difference in the birth weight of babies and neonatal complications.

DISCUSSION

Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide complicating 5 to 8% of the pregnancies. The present study focuses on prevention of this disease in order to provide requisite health care to both mother and fetus. There is strong evidence with good quality that LDA (Low Dose Aspirin) is considered a good preventive tool for pre-eclampsia. The beneficial effects of LDA include prevention of early onset disease, associated maternal complications and fetal complications. That is why many societies including American College of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), World Health Organization (WHO), American Heart Association, American Stroke Association and others agreed on recommending its use for high-risk patients.

In the present study, mean gestational age at delivery was 38.12±1.47 weeks and 38.26±1.62 weeks in group 1 and group II, respectively. On statistical analysis, the difference among both the groups found to be comparable ($p > 0.05$). A study conducted by Harrington *et al*, mean gestational age was 38.3 weeks and 38.1 weeks in aspirin and

placebo groups respectively.[12] In a study conducted by Sibai *et al*, mean gestational age was 38.6 weeks and 38.7 weeks in study (60 mg) and control group, which is comparable to our study.[13]

In present study, incidence of preterm delivery was 12% and 10% in group 1 and group II respectively. Rolinik *et al* reported incidence of preterm birth 6.5% and 7.4% respectivelyin study (150 mg) and control group. 39 In a meta-analysis conducted by Ting-ting *et al*, the incidence of preterm birth was 16.5% and 19.5% in aspirin and placebo group respectively.[14] Another study conducted by Yu *et al* incidence of preterm birth was 24.3% and 27% in interventional (150 mg) and control group respectively.[15]

In present study, 76% and 80% women went into labour spontaneously in group 1 and group II, respectively. In group 1 and II 24% and 20% women were induced. On statistical comparison, no significant difference was observed between twogroups. In a study conducted by Sibai *et al*, 16.6% and 16.7% induced respectively in interventional (60 mg) and control group.[13]

In the present study there was no statistical difference in the women who delivered vaginally and by caesarean section in the two groups. Similar study conducted by Harrington *et al*, rate of caesarean section was 19.6% and 15.9% in study and control group respectively.[12]

In present study, the incidence of pre-eclampsia was 16% and 12% in group 1 and group II, respectively making an overall incidence of pre-eclampsia of 14%. Villa *et al* reported incidence of pre-eclampsia 13.1% and 18.2% in the study (100 mg) and placebo group respectively.[16] Another study conducted by Yu *et al* reported incidence of pre-eclampsia 17.7% and 18.8% in aspirin (150 mg) and placebo group respectively.[15] In a study conducted by Zhao *et al*, incidence of pre-eclampsia was 18.6% in aspirin group (75 mg) as compared to 57.9% in placebo.[17]

In present study, incidence of preterm and term pre-eclampsia was 6% and 10% in group I. While in group II, it was 4% and 8% respectively. Caritis et al found that incidence of pre-eclampsia in preterm and term gestation 4.9% and 17.3% in study (60 mg) and placebo group respectively.[18] Similar study was conducted by Rolnik *et al*, the incidence of 1.6% and 6.6% in study (150 mg) group while Villa *et al* reported the incidence of 1.6% and 11.4% in study (100 mg) group at preterm and term respectively.[16,19]

In present study, incidence of abruption lacentae was 4% and 2% in group I and group II respectively. On statistical analysis, the difference among both the groups found to be comparable (p >0.05).

In a study conducted by Caritis *et al*, the incidence of abruption was 1% and 2% respectively in aspirin (60 mg) and control group.[18] In a meta-analysis conducted by Ting-ting *et al*, the incidence of abruption was 1.5% and 1.1% respectively in aspirin (80-100 mg) and control group.[37] In a study conducted by Yu *et al*, the incidence of abruption was 3.6% and 1.8% respectively in study (150 mg) and control group respectively.[15]

In present study, incidence of postpartum haemorrhage was 4% and 2% in group 1 and group II respectively. On statistical analysis, the difference among both the groups found to be comparable (p >0.05). In a study conducted by Bakhti *et al*, the incidence of postpartum haemorrhage was 7.3% and 2.4% respectively in aspirin (100 mg) and control group.[20] In a Meta-analysis conducted by Ting-ting *et al*, the incidence was 15.7% and 15.2% in intervention (80-100 mg) and placebo group respectively.[21]

In present study, incidence of FGR was 4% in both the groups *i.e.* group I and II. In a study conducted by Zhao *et al*, incidence was 1.3% and 3.1% in study (75mg aspirin) and placebo group respectively.[17] Another study conducted by Yu *et al* reported 1.7% and 4.3% incidence in interventional (150 mg aspirin) and placebo group respectively.[15]

CONCLUSION

Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality. It is now clear that low dose aspirin is effective in secondary prevention of pre-eclampsia in women with previous history of pre-eclampsia. In the present study, although the incidence of pre-eclampsia was more in 75 mg aspirin group in comparison to 150 mg group, but the difference was not statistically significant. Hence there is no correlation between 75 mg v/s 150 mg dose of aspirin and the incidence of pre-eclampsia in women with previous history of pre-eclampsia. Also 150 mg aspirin had no statistically significant effect on the incidence of secondary outcome (Abruptio placenta, any maternal morbidity, fetal outcome intrauterine growth restriction, intrauterine death, NICU admission, NICU stay and perinatal death) in comparison to 75 mg aspirin.

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