Section: Obstetrics & Gynaecology

Research

EFFECTIVENESS OF LOW-DOSE ASPIRIN IN PREVENTING PRE-ECLAMPSIA: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Pre-eclampsia is the most common form of hypertension that complicates pregnancy, occurring in about 3 percent of pregnancies. It is one of the leading causes of maternal and perinatal morbidity. Aspirin in low doses is used as an antiplatelet drug to reduce the risk of heart attack and stroke either by interfering with platelet adhesion or by aggregating and preventing initial clot formation. Its anti-inflammatory and antiplatelet properties make it a potential option in the management of certain pregnancy-related conditions. It may have a beneficial effect on endothelial dysfunction later in gestation. This could provide more optimal conditions for invasion of the uterine spiral arterioles and improved utero-placental blood flow, which might prevent or delay development of pregnancy-induced hypertension or preterm delivery. The present study was done to evaluate the effectiveness of low-dose aspirin (150 mg) in preventing pre-eclampsia among at risk patients. Further, we evaluated its effectiveness in preventing the adverse outcome of pregnancy like miscarriage or still-birth. **Materials and Methods:** A randomized controlled trial was done in the department of Obs & Gynecology of JNIMS, Imphal, India during the period Nov 2018 to July 2020 among conceived by 11-14 weeks who had at least one risk factor for developing pre-eclampsia. They were randomized into two groups: aspirin group and no-aspirin. The aspiring group was administered 150 mg of aspirin daily while the no-aspirin group received nothing. They were followed till the gestation age of 36 weeks. **Result:** 206 women participated in the study, half of them being in the two groups. The baseline characteristics of the women in the two groups were comparable. At the end of the study-period, 02 study-participants (1.9%) and 05 study-participants (4.9%) in the aspirin groups and no-aspirin group respectively were found to develop pre-eclampsia giving an odds-ratio of 0.38. But this was not found to be statistically significant (95% CI:0.07-2.05). Similarly, incidences of stillbirths or miscarriages between the two groups did not show any significant difference. **Conclusion:** Among pregnant women who are at risk of developing pre-eclampsia, the administration of aspirin at a dose of 150 mg per day from 11-14 weeks of gestation until 36 weeks of gestation did not result in significant lower incidence of pre-eclampsia as well as miscarriage or stillbirth when compared to no-aspirin group.

INTRODUCTION

Hypertension is a common medical problem encountered during pregnancy, complicating 5 percent to 10 percent of pregnancies. Hypertensive disorders in pregnancy are associated with higher rates of maternal, fetal, and infant mortality, and severe morbidity.[1]

Pre-eclampsia is the most common form of hypertension that complicates pregnancy, occurring in about 3 percent of pregnancies. It is one of the leading causes of maternal and perinatal morbidity.[2] Adverse pregnancy outcomes related to severe pre-eclampsia and eclampsia are caused largely by the need for preterm delivery (ACOG 2013).[1] Intra-uterine growth restriction (IUGR), placental abruption and preterm birth are common eventualities and produce associated neonatal morbidities.[3]

Aspirin (acetylsalicylic acid) is a salicylate drug often used as an analgesic to relieve minor aches and pains, an antipyretic to reduce fever, and an anti-inflammatory medication. Aspirin in low doses

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is used as an antiplatelet drug to reduce the risk of heart attack and stroke either by interfering with platelet adhesion or by aggregating and preventing initial clot formation. Its anti-inflammatory and antiplatelet properties make it a potential option in the management of certain pregnancy-related conditions.[1] It may have a beneficial effect on endothelial dysfunction later in gestation. This could provide more optimal conditions for invasion of the uterine spiral arterioles and improved utero-placental blood flow, which might prevent or delay development of pregnancy-induced hypertension or preterm delivery.[3]

Studies have shown that, in pre-eclampsia, platelet TXA2 increases significantly, whereas prostacyclin drops sharply. This imbalance is present from 13 weeks of gestation in patients at high risk.[4] TXA2/PGI2 imbalance can be reversed by 2 weeks of treatment with low-dose aspirin, which inhibits TXA2 secretion, and thus platelet aggregation,[5] without altering secretion of endothelial prostacyclin (PGI2),[6] thereby favoring systemic vasodilatation. In hypoxic conditions, aspirin inhibits the expression of sFlt-1 in human trophoblasts, and thus shows proangiogenic activity.[7] sFlt-1 is the soluble form of the VEGF receptor, which, in binding to circulating placenta growth factor (PlGF) and vascular endothelial growth factor (VEGF), behaves as a potent anti-angiogenic factor.[8] sFlt-1 is present at high levels in the circulation of patients with preeclampsia and is responsible for the angiogenic imbalance seen in the pathogenesis of preeclampsia.[8,9] Meta-analysis of related studies also has shown that, aspirin in low doses is not associated with an overall increase in the risk of congenital malformations.[10]

There is dearth of published literatures from the north-eastern part of India. Hence, it was felt important to take up this study to see whether low-dose Aspirin is effective in preventing the development of pre-eclampsia in at risk patients.

Objectives

The present study was done to evaluate the effectiveness of low-dose aspirin (150 mg) in preventing pre-eclampsia among at risk patients. Further, we evaluated its effectiveness in preventing the adverse outcome of pregnancy like miscarriage or still-birth.

MATERIALS AND METHODS

A randomized controlled trial was conducted during the period of Nov 2018 to July 2020 in the department of Obstetrics & Gynecology, JNIMS, Imphal, India which is a tertiary care hospital. The study population was taken from pregnant women attending Obstetrics & Gynecology OPD. Women who were pregnant for 11-14 weeks and who had at least one of the at known risk factors for the development of pre-eclampsia viz., nulliparity, age >35 years, prior stillbirth, assisted reproductive technologies, BMI >30, multifetal pregnancy, diabetes, prior pre-eclampsia or chronic hypertension and were willing to participate in the study were recruited. Anyone who had contraindications to aspirin were excluded from the study. The sample size calculation was based on reduction of pre-eclampsia by 89% in the aspirin group. Taking the incidence of pre-eclampsia among general pregnant ladies as 10%, with 90% power and significance level of 5% to detect this difference, the sample size calculated was 186 using Stata 9.0. Considering a probable 10% loss to follow-up, the required sample size was finalized to 206 (103 in low-dose aspirin group [A] and the remaining 103 in the control group [B]).

Block randomization was used as the sampling method. Using permutations and combinations, four sets of combinations was used namely, AABB, BBAA, ABAB and BABA. Four sets of envelope containing all the four possible combinations put inside each envelope were arranged. An envelope was randomly picked from the set of four. The participant was made to randomly pick one chit from that envelope and accordingly assigned the respective group. Similarly, for subsequent three participants, using the same envelope, same method was applied. It continued for the first four envelopes from one set. Similar method was applied for subsequent participants till our desired sample size was achieved.

A pre-tested semi-structured questionnaire consisting of demographic characteristics, detailed past obstetrics and medical history, physical and obstetrical examinations and investigations was used for data collection. The questionnaire also had a section for noting the follow-up findings.

Once enrolled, study-participants in [A] group were administered 150 mg of aspirin on daily basis at bedtime till 36 weeks of gestation while no drug was administered to [B] group. Compliance to the drug in [A] group was done by regular telephonic conversations and reminders.

All participants were followed up in OPD on monthly basis. Their blood pressures were recorded in each of the visits. If the BP in either of the arms was ≥140/90 during any visit, the participants were kept under observation for at least 4 hours and BP was measured again. If both the readings showed consistent elevation of BP, the participants were admitted and 24 hour urine examination for evidence of proteinuria (>300mg of protein/24 hour) was done to establish the development of pre-eclampsia. If any participant developed pre-eclampsia during any period of gestation, they were managed in similar fashion like other pre-eclampsia patients attending JNIMS. However, the participant was followed for secondary outcome.

USG for fetal wellbeing was done on monthly basis to rule out any miscarriage or still-birth. All the investigations required were done free of cost inside the hospital.

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Data were entered into MS-excel and completeness and consistency was checked. Later it was transferred to SPSSv20. Descriptive statistics such as percentage, median and interquartile range were used to summarize the findings. For analytical statistics, Pearson's Chi square test and Odds ratio were used to test the association between the dependent and independent variables. A p-value of <0.05 was considered statistically significant.

Ethical approval and permission to conduct the study was obtained from the Institutional Ethics Committee, JNIMS. Written informed consent was obtained from each study participant. Confidentiality was maintained during the study by giving a unique code for each study participant in each group and by not mentioning their names. All those who developed pre-eclampsia during the study were given due proper medical care after admission.

RESULTS

Completed data sets could be obtained from 206 study participants. The median age (IQR) of the [A] group participants and [B} groups participants were 29 (24-33) years and 28 (24-33) years respectively with a range of 19-40 years. The residency (urban or rural) and religion in both the study groups were comparable. Also, the other baseline characteristics in the two groups did not show any statistically significant difference. [Table 1]

Table 1: Baseline characteristics of the study-participants

Baseline characteristics	A group (n=103)	B group (n=103)	p-value
Residency (%) • Rural • Urban	 57 (55.3) 46 (44.7)	 52 (50.5) 51 (49.5)	0.557
Median POG at enrolment (IQR) in weeks	12 (11-12)	11 (11-12)	0.058
Religion (%) • Hindu • Muslim • Christian and others	 47 (45.6) 41 (39.8)) 15 (14.6)	 62 (60.2) 30 (29.1) 11 (10.7)	0.112
Past H/O pre-eclampsia (5) • Yes • No	 9 (8.74) 94 (91.26)	 9 (8.74) 94 (91.26)	1.0
H/O of chronic HTN (%) • Yes • No	 3 (2.9) 100 (97.1)	 4 (3.9) 99 (96.1)	0.701
H/O of diabetes mellitus (%) • Yes • No	 5 (4.9) 98 (95.1)	 3 (2.9) 100 (97.1)	0.471
H/O multiple pregnancy • Yes • No	 5 (4.9) 98 (95.1)	 6 (5.8) 97 (94.2)	0.757
Prior still birth • Yes • No	 5 (4.9) 98 (95.1)	 5 (4.9) 98 (95.1)	1.0

Table 2: Incidence of secondary outcomes in aspirin and no-aspirin groups

Secondary outcomes	Aspirin Group (N=103)	No Aspirin Group (N=103)	Odds Ratio (95% CI)
Pre-eclampsia (%) • No • Yes	 101 (98.1%) 2 (1.9%)	 98 (95.1%) 5 (4.9%)	0.38 (0.07-2.05)
Stillbirths/Miscarriages (%) • No • Yes	 100 (97.1) 3 (2.9)	 100 (97.1) 3 (2.9)	1.00 (0.19-5.07)

There were no any adverse events that occurred in either the aspirin or no-aspirin groups of participants during the entire course of study.

During follow-up period, 02 study-participants (1.9%) and 05 study-participants (4.9%) in the aspirin groups and no-aspirin group respectively were found to develop pre-eclampsia giving an odds-ratio of 0.38. But this was not found to be statistically significant (95% CI:0.07-2.05). Similarly, incidences of stillbirths or miscarriages between the two groups did not show any significant difference. [Table 2]

DISCUSSION

In this Randomized Controlled Trial, involving pregnant women who were at risk for the development of pre-eclampsia, the administration of Aspirin at a dose of 150 mg per day from 11-14 weeks of gestation until 36 weeks of gestation was not associated with a significant lower incidence of pre-eclampsia when compared to no-aspirin group. There was no significant between-group difference in the incidence of secondary outcome of stillbirth or miscarriage. These findings were consistent with

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the study findings made by Rotchel YE et al,[11] Obido AO et al,[12] Subtil D et al,[13] Byaruhanga RN et al,[14] and Chiaffarino F et al.[15]

However, studies conducted by Vainio M et al,[16] Lambers MJ et al,[17] Moore GS et al,[18] Sibai BM et al,[19] demonstrated that, the use of low-dose aspirin in pregnant women who were at risk of developing pre-eclampsia was associated with a significant reduction in the incidence of pre-eclampsia as compared to women who took placebo or no aspirin. Differences in time-zone, study setting, design of the study and other socio-demographic variables might explain the discrepancy in the study-findings

Decisions regarding the gestational-age range at the onset of treatment (11-14 weeks of gestation) and the primary outcome measure were informed by the results of meta-analysis suggesting that aspirin confers greater benefit if it is started at or before 16 weeks of gestation and that prevention is confined to preterm pre-eclampsia.[20,21,22]

CONCLUSION

In conclusion, this randomized controlled trial showed that among pregnant women who are at risk of developing pre-eclampsia, the administration of aspirin at a dose of 150 mg per day from 11-14 weeks of gestation until 36 weeks of gestation did not result in significant lower incidence of pre-eclampsia as well as miscarriage or stillbirth when compared to no-aspirin group.

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