Original Article

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Expectant Management of Severe Preeclampsia in Pregnant Women Remote from Term: A Randomised Controlled Study

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Abstract

Introduction: Severe preeclampsia remote from term, a clinical challenge arises in the 0.3% of pregnancies in which hypertension develops before 34 weeks. The decision to deliver at early gestational age (GA) requires weighing the risks of iatrogenic prematurity against the risks of prolonging the pregnancy which is also called expectant management. *Aims & Objectives:* To study the effect of expectant management of severe peelcampsiaon pregnancy outcome. *Material and Methods:* Patients presenting with signs and symptoms of severe preeclampsia presence of 2+ or more proteinuria on dipstick, Systolic blood pressure >/=160 mm of Hg and diastolic blood pressure >/=100mm of Hg, presence of one or more imminent signs of eclampsia) and gestational age 26-34 weeks were randomised (into either G1(n=50) i.e. expectant management group or G2 (n=55) aggressive management group) after thorough clinical examination, laboratory testing, ultrasonography. *Results:* Parameters such as age, parity, body mass index, gestational age, blood pressure at admission, presence of imminent signs and all laboratory investigations are similar in both the groups.The mean prolongation of pregnancy was 9.9 in the expectant group, with an averagefetal weight gain of 150 gms. There is significant (p<0.005) improvement in neonatal survival, birth weight, need for NICU stay and ventilatory support without maternal morbidity in expectant group. *Conclusion:* Though there are controversies between the previous randomised studies, our study established a higher perinatal survival and birthweight without causing increased morbidity to mother and neonate especially in neonates <30 wks GA

Keywords: Expectant Management; Perinatal Mortality; Stillbirth; Severe Preeclampsia; 26-30 Weeks.

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Introduction

According to World Health Organization, hypertensive disorders are the leading cause of maternal mortality, accounting for 16.1% of maternal deaths in developed countries over the past two decades [1]. In India, hypertensive disorders of pregnancy is the cause for 7% all maternal deaths [2].

Hypertensive disorders occur in 12% to 22% of all pregnancies worldwide, andinclude a spectrum of diagnoses that are categorized by gestational age (GA) at onset of disease and the presence of proteinuria [3-7].

Preeclampsia defined as new onset of hypertension after 20 weeks (wks) of gestation and presence of proteinuria, occurs in 5% to 8% of pregnancies [4,7,8] severe preeclampsia (SPE) is diagnosed in only 0.6% to 1.2% [9-11]. Severe preeclampsia is defined by systolic blood pressure (BP) greater than 160 mm Hg or diastolic pressure greater than 110 mm Hg and proteinuria greater than 3 g over 24 hours or 3+ on urine dip, with or without clinical or laboratory evidence of end-organ damage [4]. The

incidence of severe preeclampsia at <34 wks is 0.3 percent [5].

Severe preeclampsia is a complex disease with a chronologically unpredictable and progressively deteriorating course. There is almost no controversy regarding delivery as an ultimate treatment for severe preeclampsia in women at term or near term.

Severe preeclampsia may evolve into many complications which include seizures (eclampsia), placental abruption, disseminated intravascular coagulation, renal failure, hepatic hematoma or rupture, pulmonary edema, acute respiratory distress syndrome, retinal detachment, myocardial infarction, pancreatitis, stroke, and death. Fetal complications include intrauterine growth restriction, hypoxia-acidosis, oligohydramnios, long-term neurologic morbidity, and fetal demise. The current standard of care, therefore, includes prompt delivery of patients with SPE if the disease develops at or after 34 wks GA [12].

SPE remote from term, a clinical challenge arises in the 0.3% of pregnancies in which SPE develops before 34 wks GA [13]. The decision to deliver at early GA requires weighing the risks of iatrogenic prematurity against the risks of prolonging the pregnancy also called expectant management. Numerous authors have suggested varying degrees of expectant management to improve perinatal outcomes. In countries like India where perinatal mortality is high, it is a serious concern for maternal and fetal morbidity

Only3 randomized trials have been reported [14,15,16]. Two studies reported improved perinatal outcomes with minimal maternal morbidity with expectant management. There have been minimal observational studies regarding the above said problem in India, hence this study was incited.

Aims & Objectives

1. To study the effect of expectant management of severe hypertension on pregnancy outcome
2. To assess the feasibility of expectant management in tertiary care hospital

Material and Methods

Patients presenting with signs and symptoms of severe preeclampsia(n=105) were randomised after thorough clinical examination, laboratory testing, ultrasonography and after taking consent. The study was approved by the appropriate ethical boards.

The inclusion criteria for defining severe preeclampsia were

- Presence of 2+ or more proteinuria on dipstick
- Systolic blood pressure(SBP) >/=160 mm of Hg and diastolic>/=100mm of Hg (blood pressure was measured by auscultatory method in sitting position to nearest even number and mean of 2 readings spaced half an hour taken)
- Presence of one or more imminent signs of eclampsia [blurring of vision, severe frontal headache not responding to simple analgesics, epigastric pain not responding to antacids, oliguria defined as urine output<35ml/hour, laboratory investigations showing HELLP syndrome i.e. haemolysis on peripheral smear, elevated liver enzymes and low platelet counts <1,00,000]

Patients having severe intrauterine growth restriction (>4wks disparity), intrauterine fetal death, eclampsia, multiple pregnancy, women in labor, premature rupture of membranes, who need immediate delivery were excluded. The gestational age was calculated based on date of last menstrual period or first trimester ultrasonography or both. Patients of gestational age of 26 0/7 wks to 33 6/7 wks were included. The laboratory parameters included complete blood picture, proteinuria by dipstick, liver function tests with liver enzymes aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase(ALP), serum uric acid, blood urea, serum creatinine, clotting time, bleeding time. Thyroid function tests, coagulation profile and screening for antiphospholipid antibodies were done in in necessary patients. Complete clinical examination included obstetrical evaluation, neurological evaluation and fundoscopy.

All were admitted to the high-risk unit and blood pressure was stabilised either with oral labetalol, nifedipine or intravenous labetalol drip as appropriate. Magnesium sulphate 14gm (intravenous 4 gm and 10gm intramuscular) loading dose and 5 gm maintenance intramuscular dose was given every 4th hourly to prevent seizures [17]. Betamethasone 12mg intramuscularly was given in 2 doses 24 hours apart to accelerate fetal lung maturity [18]. Depending on the general condition of mother and fetus and patient's choice, these women were either randomised into aggressive treatment group G1(n=55) or expectant management group G2 (n=50). Patients in aggressive group after stabilisation of blood pressure were either induced to labor with extra amniotic ethacridine lactate installation or vaginal misoprostol or caesarean section as per labor room

protocol and on maternal and fetal general condition. Patients in expectant management group were stabilized and monitored [19].

The protocol for monitoring was

- Blood pressure and symptoms of imminent eclampsia (headache, blurring, epigastric pain) every 4 hourly, except when she was sleeping soundly
- Maternal weight, urine albumin, urine output measurement daily
- Daily fetal kick count
- Preeclampsia profile (complete blood picture, clotting time, bleeding time, liver function tests with enzymes, serum creatinine) twice weekly or more frequently when required
- Biweekly non-stress test
- Doppler velocimetry and biophysical profile, growth scan weekly

Expectant management was discontinued in one or more of the following situations [20,21].

Maternal Indications

- Persistent severe hypertension unresponsive to medical therapy (maximum doses of 2 antihypertensive)
- Severe headache (i.e., incapacitating, "the worst headache of my life") or persistent progressive headache (despite analgesia), visual aberrations, or epigastric/right upper quadrant pain
- Eclampsia
- Retinal detachment
- Pulmonary edema
- Renal failure with a marked rise in serum creatinine and/or urine output less than 30ml/hour for two hours unresponsive to hydration with two intravenous boluses of 500 mL fluid

Fetal Indications

- Non-reassuring fetal testing (non-reassuringnon-stress test or biophysical profile score)
- Intrauterine growth restriction (> 4wks disparity)
- Oligohydramnios with AFI <5.0 cm
- Persistent absent or reversed diastolic flow on umbilical artery Doppler velocimetry
- Intrauterine fetal death

Obstetric Indications

- Abruptio placentae
- Preterm labor
- Preterm premature rupture of membranes

Laboratory Abnormalities

- Increasing Aminotransferases levels twice the upper limit of normal
- Progressive decrease in platelet count to less than 100,000

Mode of delivery was decided on basis of bishop score, indication, maternal condition and expected fetal prognosis after discussion with the neonatologist. Mother and neonate were followed up and condition recorded.

Data Analysis

Data collected was analysed with the help of independent student T test (continuous variables with normal distribution), Fisher's Exact Test (Univariate comparisons of dichotomous data), Pearson chi-square tests from SSIS 21.0 version software. The p value<0.05 was taken as statistically significant.

Results

Parameters such as age, parity, body mass index, gestational age, systolic blood pressure(SBP), diastolic blood pressure (DBP) at admission, presence of imminent signs at admission and all the above said laboratory investigations are comparable in both the groups, so it makes both the groups similar (Table 1).

The mean systolic blood pressure at admission was 181.8±15 mm Hg, diastolic blood pressure 108.9±7.6 mm Hg.

Five women (10.0%) from expectant group and 8 women (14.5%) from aggressive group had preeclampsia superimposed on chronic hypertension. Antihypertensive usually started were labetalol as the first line and nifedipine was added if control of blood pressure is not achieved. Fifteen women from expectant group and 13 women from aggressive group needed intravenous labetalol for control. Fundoscopy was normal in most of the women , 2 women from G1and 2 women from G2 had grade 2 hypertensive retinopathy changes, 3 women from G1and 7 women from G2 had grade 1 hypertensive retinopathy changes, none had

progression or symptoms of retinal detachment throughout the course in hospital. Twenty eight (52%) women from expectant group and 32 (58%) women from aggressive group had anemia [22] (Hb<11 gm%). All women in expectant group received 2 doses of betamethasone coverage whereas only 10(18.2%) women in aggressive group received the full course.

The various indications of termination in the expectant group were new onset of imminent signs (7), severe oligohydramnios (7), uncontrolled hypertension (6), spontaneous onset of labor (6) eclampsia (5), abruption (5), prelabour rupture of membranes (3), persistent non-reactive non stresstest (3), abnormal doppler(3),decreased fetal movements (2), severe growth restriction (2), and HELLP syndrome (1).

Most of the women had vaginal deliveries 78 (74.3%), 17 (34%) in expectant group and 10 (18%)in aggressive group had caesarean section. There were few neonates who died with very poor Apgar before shifting to NICU and stillbirths n=23, of these 12 (24%)were from expectant group and 11(20%) were from aggressive group. 81 neonates (77.1%) required NICU admission, 37 in G1and 44 in G2. Fifty seven babies needed ventilatory support 21 in G1and 36 in G2. The neonatal complications were hyaline membrane disease (n=20 in G1 and n=20 in G2) respiratory distress (n=9 in G1 and n=12 in G2), sepsis (n=14 in G1 and n=16 in G2), birth asphyxia (n=4 in G1 and n=16 in G2), necrotising enterocolitis (n=5 in G1 and n=18 in G2) intraventricular haemorrhage (n=2 in G1 and n=4 in G2) neonatal jaundice (n=9 in G1 and n=8 in G2) anaemia (n=3 in G1 and n=1 in G2). Twenty babies (19%) died on ventilatory support due to various reasons of which 4 belonged to the expectant group and 16 from the aggressive group.

Sixty two (59%) babies were sent home of which 34 (68%) were from expectant group and 28 (50.9%) were from aggressive group.

Maternal complications included blood transfusions (n=6 G1 n=12 G2), HELLP syndrome (n=1 G2), persistent high blood pressure (n=5 G1 n=3 G2), platelet transfusion (n=1 G2), postpartum haemorrhage (n=2 in G1 n=5 in G2 wound infection (n=1 in G1). Two patients developed postpartum eclampsia and pulmonary edema and were electively ventilated(n=1 G1 n=1 G2). One patient developed Disseminated intravascular coagulation after

Table 1: Maternal parameters P value<0.05 taken as significant

Parameter	Expectant group n=50	Aggressive group n=55	P Value
Age (years)	22.5±3.6	22.7±3.9	0.81
Body mass index	24.7±3.1	24.6±2.2	0.08
Gestational age in days	213.9±15.9	209.1±15.4	0.34
Systolic blood pressure in mm Hg	182.4±16.0	181.2±14.0	0.33
Diastolic blood pressure in mm Hg	108.9±7.8	109.0±7.5	0.96
Hemoglobin in gm%	10.4±1.1	9.7±1.2	0.51
Packed cell volume	30.9±2.8	31.7±2.3	0.76
Serum bilirubin mg/dl	0.5±0.2	0.5±0.4	0.23
Serum uric acid mg/dl	5.5±0.9	5.9±0.9	0.94
Platelets× 10^3 per microliter	147.3±46.7	143.0±48.0	0.55
Serum creatinine mg/dl	0.7±0.1	0.7±0.1	0.16
Blood urea mg/dl	31.9±8.7	34.0±7.5	0.21
Fetal weight on ultrasound in gms	1001.8±269	983.5±217	0.09
Amniotic fluid index	8.2±2.4	8.2±2.8	0.82
Primi gravid n (% of group)	29(58%)	38(69.1%)	
Multigravida n (%of group)	21(42%)	17(30.9%)	
Proteinuria	35(70%)	40(72.7%)	
2+ (500 - 1500 mg/24 hours)	11(22%)	13(23.6%)	
3+(over 2500 mg/24 hours)	4(8%)	2(3.6%)	
4+ (over 3000 mg/24 hours)			
Total duration of admission in days	27.5±11.4	25.8±12.2	0.697

Table 2: Neonatal parameters. P value<0.05 taken as significant

Parameter	Expectant group N=50	Aggressive group N=55	Sig.
Prolongation of pregnancy in days	9.9±4.8	0.9±0.6	0.0001
Baby weight at delivery in gms	1147±298	961±227	0.04
Ventilatory support	21(42%)	36(63.2%)	0.013
Average no of days NICU admission	11.6±7.0	17.8±9.9	0.028
Perinatal mortality	16(32%)	27(49.1%)	0.017
Still birth	12(24%)	11(20%)	0.22

Table 3: Comparison between the randomised studies

Parameter	Odendaal etal 1990	Sibai etal 1994	MEXPRE 2013	Present Study
N	18	46	133	50
Gestational age in weeks	26-34	28-34	28-33	26-34
Average prolongation of pregnancy in days	7.1	15(3-32)	10.3	9.9
Perinatal death %	16.6	0	8.7	32
Still birth%	5.5	0	-	24
Mean birth weight gms	1420	1622	1659	1147

Table 4: Survival of neonates by gestational age

Parameter	Expectant Group n=50	Aggressive Group n=55
Neonatal mortality 26-30 wks n(%)	15(93.75)	25(92.59)
Neonatal mortality 30-34 wks n(%)	1(6.25)	2(7.40)
Total n(%)	16(100)	27(100)

placental abruption and succumbed to multiorgan failure and death (G2)

During followup (1 year) 9 babies developed cerebral palsy and delayed milestones (n=4 G1, n=5 G2), hypoxic ischemic encephalopathy(HIE) with cerebral palsy (n=1 G1), and HIE grade 1 (n=3 G2).

Discussion

There is ample evidence stating that perinatal mortality is indirectly proportional to the gestational age, birth weight and administration of corticosteroid for lung maturity. In cases where delivery is mandatory for maternal health, the common logical practice is to terminate the pregnancy regardless the perinatal outcome. With improvement in neonatal care, and high-risk pregnancy units, there seems to be hope for very low birth weight and preterm neonates.

Although the ideal GA for delivery is after 37 completed wks, many studies demonstrated good perinatal outcome after 34 weeks [23]. Very high perinatal mortality has been reported in women with SPE before 34 weeks ranging from 238-313 per 1000 live births [24,25,26]. There are three randomised controlled studies reported for expectant management of severe preeclampsia [14,15,16] (table 3).

There is a high still birth rate in both groups in our study 24% in G1, this correlates with the observational studies in SPEwhich include Abdella etal [27] (26.25%), Railton and Allen (14.9%), Lin etal [28] (9.55%). The authors found a stillbirth to neonatal death rate of 2.9, in our study the ratio in G1 is 3 and G2 0.7. This reversed ratio in two groups may be because many neonates from G2 expired in NICU. The still birth rate in G1 is 24% as compared to G2 20%, this rate corresponds to the still birth rate for preterm infants in developing countries [29], moreover many women in the study group had clinical growth restriction too.

Gestational age at delivery was significantly higher in G1 than G2 ($p<0.005$). The mean prolongation of pregnancy was 9.9 in the expectant group. This prolongation and completion of corticosteroid dose may be the reason for the significant perinatal mortality rate in both the groups($p<0.005$) (Table 3). The mean weight gain in expectant group is about 150.7gms. This value was obtained from subtracting the predicted birthweight by ultrasound at randomisation and actual birth weight. This significant weight gain ($p<0.005$) may be one of the other reason for improved perinatal outcome.

In contrast to the previous studies most of the women in our cohort were delivered vaginally. The 1 minute APGAR score was significantly better ($p<0.005$) in the expectant group, although after prompt resuscitation the 5 minute APGAR was same (Table 2) the babies who required ventilation, duration of NICU stay were also significantly less in the expectant group ($p<0.005$). Once again this can be attributed to the prolongation and steroid administration.

Perinatal mortality however is very higher compared to the previous studies (Table 3), this can be attributed to the general causes like anaemia, and very low birth weight, the mean birth weight being only 1147gms. whereas MEXPRE study [16] reported a mean wt of 1659gms, Odendaal etal [14] reported a mean wt 1420gms and 1622gms in study conducted by Sibai etal [15]. The high perinatal mortality rate however corresponds to the GA and birthweight of Indian neonates [30].

When we divided the neonatal mortality based on the GA> 30 wks we observed that only one neonate from G1 and 2 from G2 expired (Table 4). This correlates with the observation made by MEXPRE study [16]. The improvement in the neonatal outcome in <30 wks neonates in G1 may be due to weight gain, steroid administration, constant observation, close monitoring and treating hypertension and anaemia.

Long term complications for the neonate like cerebral palsy and HIE were similar in both the groups [31], however maternal complications like persistent hypertension, anaemia, need for blood transfusions were more in the expectant group. ($p<0.005$). there were two women,one from each group who developed post partum eclampsia and pulmonary edema who were electively ventilated, both recovered well. One woman from aggressive group had severe blood loss after abruption,and in spite of 17 blood transfusions and ventilatory support she deteriorated and developed DIC and died of multiorgan failure.

Though Odendaal etal [14] had the incidence of abruption higher in the aggressive group andMEXPRE study [16] reported more abruption in expectant group, our study had 5 cases in both groups. Its seems logical that expectant group will have less abruption inview of frequent monitoring, but it is not so in our group.

In contrast to the earlier studies, we have recruited women with even a single dose of corticosteroid as recent evidence advocates administration of a single dose of corticosteroid, although repetition of the dose after one week remains controversial [32]. This might be the weakness of the study.

Conclusion

Though there are controversies between the previous randomised studies, our study established a higher perinatal survival and birthweight without causing increased morbidity to mother and neonate. Beyond, there is less need for ventilatory support and NICU stay in these neonates which is very important in the overburdened NICU in India. Although the importance of expectant management in babies more than 30 wks seems less, it may be more useful in babies less than 30 wks. Finally, these subsets of women need continuous monitoring in high risk units as they deteriorate fast with minimal warning signs. This level of tertiary care should be extended to all the peripheral centres where more than half of Indian population resides.

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