Confounders for Neonatal Intensive Care Unit Admission of Neonates Born to Mothers Who Had Preeclampsia

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ABSTRACT

OBJECTIVE: The aim of this study was to investigate the effect of some maternal and neonatal clinical parameters on the neonatal intensive care unit admission rates of neonates born to mothers who had preeclampsia.

STUDY DESIGN: Study included 402 singleton pregnant women with preeclampsia who admitted to Maternal-Fetal Medicine Unit of Zeynep Kamil Children and Women's Health Training and Research Hospital. Pregnancies with uterine rupture, chorioamnionitis and congenital malformations were excluded. Some maternal and neonatal clinical characteristics were assessed to predict neonatal intensive care unit admission.

RESULTS: Among 402 neonates, 140 (35%) of them had an indication for neonatal intensive care unit admission, among 140 neonates, 136 (97%) of them were preterm neonates. Comparison of groups with and without neonatal intensive care unit admission indicated significant differences between groups in terms of gestational age, Apgar scores at 1st and 5th minutes, birth weight, some maternal laboratory parameters (Hemoglobin, hematocrit, alanine aminotransferase, aspartate aminotransferase, albumin). In multivariate analysis, among all study population, gestational age at delivery, birth weight and Apgar scores were found to be significantly associated with neonatal intensive care unit admission. On the other hand, in subgroup of term neonates, none of the variables was shown to be associated with neonatal intensive care unit admission.

CONCLUSION: Gestational age at delivery and the birth weight are the main risk factors for neonatal intensive care unit admission of neonates born to mothers who had preeclampsia.

Keywords: Labor induction, Magnesium sulfate, Neonatal intensive care unit, Preeclampsia

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Introduction

Most common causes for neonatal intensive care unit (NICU) admission include prematurity, maternal infection, respiratory failure, jaundice, neonatal infection, and congenital malformation. In addition to these well-defined causes, there are still several NICU admissions that are unanticipated at the time of delivery (1,2). Preeclampsia is a major contributor to the maternal and neonatal mortality and morbidity. It is the 2nd largest cause of maternal mortality worldwide and affects 5% to 7% of pregnant women worldwide (3-6). Preeclampsia is generally defined as the development of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman, although different variations of this have been proposed by different groups and organizations (ACOG, ISSHP, Australian college) (5,6). Among all pregnant women, approximately 5% of the deliveries are required to be managed under eclampsia prophylaxis each year. Majority of the obstetricians prefer magnesium sulfate (MgSO4) as the first choice medication for eclampsia prophylaxis. MgSO4 was shown to be associated with smooth muscle relaxation. Neuroprotective effect of MgSO4 in preterm fetus is a well-known issue, some studies showed MgSO4 administration before delivery to be associated with increased rate of NICU admission among term fetuses (7,8).

The aim of this study was to investigate the effect of some maternal and neonatal clinical parameters on the neonatal in-

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tensive care unit admission rates of neonates born to mothers who had preeclampsia.

Material and Method

This prospective cohort study included 402 singleton pregnant women with preeclampsia who admitted to Maternal-Fetal Medicine Unit of Zeynep Kamil Children and Women's Health Training and Research Hospital between February 2017 and April 2018. This study was performed in accordance with the Declaration of Helsinki (1964), as revised in 2013 and approved by the Ethics Committee of the institutional review board. Written informed consent was obtained from each participants. Pregnancies with uterine rupture, chorioamnionitis and congenital malformations were excluded. Some maternal and neonatal clinical characteristics were assessed to predict neonatal intensive care unit admission.

All singleton pregnancies diagnosed with preeclampsia were recruited for the study. All neonates in the current study were born to mothers with preeclampsia. Majority of the cases received MgSO4 for eclampsia prophylaxis before delivery and/or after delivery.

Preeclampsia was defined as a patient exhibiting hypertension with proteinuria. The criteria for both MgSO4 administration and NICU admission were based on the judgment of the medical providers. For women with preeclampsia and sustained systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, antihypertensive therapy was recommended, additionally, in pregnant women with chronic hypertension and no end-organ damage, no antihypertensive therapy is needed if systolic blood pressure <160 mmHg or diastolic blood pressure <105 mmHg. In pregnant women with chronic hypertension who are on antihypertensive therapy, blood pressure was maintained between 120/80 mmHg and 160/105 mmHg (10).

Labor induction was indicated based on the maternal-fetal well-being and in cases with hypo-contractile uterine activity. Participants were considered to be symptomatic if they reported swelling (edema), headache, nausea or vomiting, abdominal (stomach area) and/or shoulder pain, lower back pain, sudden weight gain, changes in vision, hyperreflexia, shortness of breath, anxiety.

Cases with abnormal laboratory tests were determined according to the presence of one or more abnormal results for liver and kidney function tests. Abnormal liver and kidney function tests and serum albumin levels were considered in cases with levels out of reference ranges (i.e. # of platelets <100x103, AST ≥2 x max limit (AST ≥70 U/L), creatinine ≥1.5 mg/dL, intravascular hemolysis (LDH ≥600 U/L, total bilirubin ≥ 1.2 mg/dL). The primary outcome was NICU admission at any time before the hospital discharge. Some maternal and neonatal clinical and laboratory parameters were assessed between cases with and without NICU admission.

Statistical analysis

Analysis were carried out by SPSS version 15. Statistical comparison was carried out by Student-t, and chi- squared test. Multivariate regression analysis was used to determine adjusted associations. Where appropriate, a p-value (two-tailed) of <0.05 was considered significant.

Results

Among 402 neonates, 140 (35 %) of them had an indication for NICU admission, among 140 neonates, 136 (97%) of them were preterm neonates. Some demographic and clinical parameters of whole study population were summarized in table 1 and 2.

Table 1: *Summary of some demographic characteristics of the whole study population*

	Minimum	Maximum	mean ± SD
Age (Years)	17	47	30.2±6.4
Gravidity	1	16	2.5±1.8
Parity	0	11	0.9±1.1
BMI (kg/m^2)	20.2	49.6	30.7±5.1
Gestational age at delivery (weeks)	27	42	35.9±3.1
Birth weight (g)	670	4400	2675.3±736.6
Duration of maternal hospital stay (days)	2	17	3.7±1.6

BMI: Body mass index, SD: Standard Deviation

Table 2: *Summary of some maternal laboratory characteristics of the whole study population*

	Minimum	Maximum	Mean ± Standart Deviation
Hb (g/dL)	7.1	15.1	11.2±1.5
Htc (%)	19.7	43.9	33.8±4.5
Plt (10^3)	21	491	204.8±69.7
BUN (mg/dL)	2.1	34	9.2±3.7
Creatinine (mg/dL)	0.03	4.8	0.67±0.3
ALT (U/L)	6	345	29.1±36.06
AST (U/L)	6	339	32.2±34.4
LDH (iu/L)	17	657	233.4±91.1
Albumin (g/dL)	1.3	4	2.9±0.4

Hb: Hemoglobin, Htc: Hematocrit, Plt: Platelet, BUN: Blood urea nitrogen, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, LDH: Lactate dehydrogenase

Comparison of groups with and without NICU admission was shown in table 3 which indicated significant differences between groups in terms of gestational age,

Apgar scores at 1st and 5th minutes, birth weight and some laboratory parameters (Hemoglobin, hematocrit, alanine aminotransferase, Aspartate Aminotransferase, albumin). Smoker rates were similar between groups (3.5% vs. 3.8%, $p>0.05$). Groups had similar rates of family history for preeclampsia (5.7% vs. 5.3%, $p>0.05$). Group with NICU admission had significantly higher rate of regular follow-up (80% vs. 69%, $p<0.05$). Cesarean section rate was significantly higher in group with NICU admission (88% vs. 71%, $p<0.05$). Neonatal sex rates were similar between the two groups (46.4% vs. 53% male, $p>0.05$). Eclampsia prophylaxis with MgSO4 was more commonly indicated in group with NICU admission (73% vs. 56%, $p<0.05$). Antihypertensive medication was more commonly indicated in group with NICU admission (65% vs. 38%, $p<0.05$). Preeclamptic symptoms were more commonly observed in cases with NICU admission (70% vs. 53%, $p<0.05$). Labor induction was less commonly indicated in group with NICU admission (44% vs. 61%, $p<0.05$). There were 15 cases with uncontrolled hypertension with accompanying abnormal laboratory tests, among these cases 9 (60%) of them required NICU admission ($p<0.05$). In multivariate regression analysis, among all study population, gestational age delivery, birth weight and Apgar scores were found to be significantly associated with NICU admission (Table 4). On the other hand, in subgroup analysis of term neonates, none of the variables was shown to be associated with NICU admission (Table 5). While both Apgar scores at the first and fifth minutes were significantly associated with NICU admission in subgroup analysis of preterm neonates (Table 6).

Table 3: *Comparison results of groups with and without NICU admission in terms of some demographic and clinical parameters*

	Mean ± Std Deviation		*p* Value
	With NICU Admission (n: 140)	Without NICU Admission (n: 262)	
Age (Years)	30.1 ± 6.09	30.2 ± 6.7	NS
Gravidity	2.4 ± 2.03	2.5 ± 1.7	NS
Parity	0.8 ± 0.9	1.01 ± 1.2	NS
BMI (kg/m2)	30.6 ± 4.6	30.7 ± 5.3	NS
Gestational age at delivery (weeks)	32.8 ± 2.5	37.6 ± 1.9	<0.05
Birth weight (gr)	1979.03 ± 609.6	3048.8 ± 484.8	<0.05
Hb (g/dl)	11.7 ± 1.6	10.9 ± 1.4	<0.05
Htc (%)	35.3 ± 4.6	33.09 ± 4.3	<0.05
Plt (103)	200.08 ± 67.6	207.3 ± 70.8	NS
BUN (mg/dL)	9.5 ± 3.3	9.3 ± 3.9	NS
Creatinine (mg/dL)	0.7 ± 0.1	0.7 ± 0.4	NS
ALT (U/L)	36.9 ± 39.3	24.8 ± 33.4	<0.05
AST (U/L)	37.9 ± 39.2	29.2 ± 31.3	<0.05
LDH (iu/l)	229.7 ± 77.8	235.4 ± 97.6	NS
Albumin (g/dl)	2.7 ± 0.4	2.9 ±0.4	<0.05
Duration of hospital stay (days)	3.9 ± 1.8	3.5 ± 1.5	<0.05

NICU Admission: Neonatal intensive care unit admission, Hb: Hemoglobin, Htc: Hematocrit, Plt: Platelet, BUN: Blood urea nitrogen, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, LDH: Lactate dehydrogenase

Table 4: *Multivariate regression analysis results to assess adjusted associations between some variables and NICU admission*

	Unstandardized Coefficients		Standardized Coefficients	*p* Value
	B	Std. Error	Beta	
(Constant)	4.117	.322		.000
Regular follow-up	.039	.034	.036	.254
Gestational age	-.047	.011	-.311	.000
Route of delivery	-.016	.037	-.015	.661
Apgar score (1st min)	-.162	.024	-.509	.000
Apgar (5th min)	.060	.026	.164	.020
Birth Weight	.000	.000	-.189	.009
MgSO4 administration	-.065	.101	-.066	.519
Antihypertensive use	.019	.037	.020	.60
Labor induction	-.053	.031	-.056	.089
Preeclamptic symptoms	-.006	.097	-.006	.950
UCHT + abnormal lab	.057	.083	.023	.496

UCHT: Uncontrolled hypertension, lab: Laboratory

Table 5: *Multivariate regression analysis results to assess adjusted associations between some variables and NICU admission in subgroup of term neonates*

Model		Unstandardized Coefficients		Standardized Coefficients	*p* Value
		B	Std. Error	Beta	
1	(Constant)	1.589	.203		.000
	Regular follow-up	.003	.028	.010	.903
	Route of delivery	.028	.029	.080	.335
	Apgar score (1st min)	-.017	.039	-.088	.670
	Apgar (5th min)	-.047	.046	-.216	.304
	MgSO4 administration	-.033	.086	-.104	.699
	Antihypertensive use	.003	.031	.008	.931
	Labor induction	-.027	.027	-.082	.333
	Preeclamptic symptoms	.019	.082	.061	.814
	UCHT + abnormal lab. findings	-.008	.114	-.006	.944

UCHT: Uncontrolled hypertension, lab: Laboratory

Table 6: *Multivariate regression analysis results to assess adjusted associations between some variables and NICU admission in subgroup of preterm neonates*

	Coefficients			
	Unstandardized Coefficients		Standardized Coefficients	Sig.
	B	Std. Error	Beta	
(Constant)	2.552	.225		.000
Regular follow-up	.098	.058	.084	.090
Route of delivery	-.109	.063	-.089	.085
Apgar score (1st min)	-.237	.031	-.759	.000
Apgar (5th min)	.068	.034	.195	.049
MgSO4 administration	.042	.165	.040	.798
Antihypertensive use	.098	.061	.098	.108
Labor induction	-.073	.050	-.073	.14
Preeclamptic symptoms	-.113	.162	-.109	.484
UCHT + abnormal lab. findings	.162	.115	.073	.160

UCHT: Uncontrolled hypertension, lab: Laboratory

Discussion

In this study, we aimed to figure out the predictors of neonatal intensive care unit admission for the neonates born to mothers who had preeclampsia. Our data showed that, after adjustment for other possible parameters, gestational age at delivery, the birth weight and both Apgar scores were found to be associated with high risk for NICU admission. In subgroup analyses of term neonates, there were only 4 cases who required intensive care, none of the parameters was associated with high risk for NICU admission in this subgroup of neonates. Consistent with our result, Habii et al showed that pregnancies with preeclampsia or gestational hypertension that delivered between 35 and 37 weeks of gestation had higher rates of neonatal intensive care unit admission, and authors claimed this result to be free from the severity of the hypertensive disease (10). It is well known that preeclamptic pregnant women are required to be managed under eclampsia prophylaxis, previous study showed that, antenatal MgSO4 exposure was associated with a significantly greater NICU admission rate (7). Again due to obtain better maternal-fetal outcome, labor induction is indicated in some cases. Free from pregnancy complications, recently published study showed induction of labor to be associated with increased risk for NICU admission (11). Previous study showed similar outcome between groups with elective versus medically indicated inductions of labor (12). In our study, we did not show any association between eclampsia prophylaxis, labor induction, abnormal laboratory tests, uncontrolled hypertension and neonatal outcome when adjusted for the gestational at delivery and the birth weight. On the other hand, in contrast to our findings, regular prenatal care was proposed to result in decreased NICU admission rate (13). Although a recent study from Amman showed that lower gestational age, lower birth weight, delivery by caesarean section were statistically significant risk factors for NICU admission (14), a majority of the NICU admissions, especially for the cases with term deliveries are unanticipated (15). Some preventive measures can be introduced for modifiable factors if they are well documented so that neonatal morbidity and mortality may be decreased with lesser financial burden. In addition, cesarean delivery was shown to be associated with an increased risk of NICU admission in our study. Overweight and obese women were reported more likely to have increased birth weight compared to infants of normal weight women, but Apgar scores, admission to the NICU, or length of postnatal hospital stay among groups were similar (16). In our study population mean maternal BMIs were similar between groups. Hypertensive disorders not requiring treatment with anti-hypertensive medication was not shown to result in increased risk for NICU admission (17,18). As we mentioned above some cases needed to undergo antihypertensive treatment to

prevent maternal complication, we did not find any impact of antihypertensive medication on NICU admission rates, on the other hand, another data showed poorly controlled chronic hypertensive disorders to result in premature deliveries (19) which may lead to increased prematurity rates among this group. On the other hand, anti-hypertensive medication was found to be a potential risk factor for NICU admission, furthermore maternal blood pressure control by antihypertensive administration did not improve pregnancy outcome in women with hypertension (20). Mean gestational age at delivery in our series cases under antihypertensive medication was significantly lower than the cases without under medication (35 vs. 37 weeks, $p < 0.05$). As a result, after adjustment for gestational age at delivery, antihypertensive use alone was not found to be associated with NICU admission. To the best of our knowledge, this is the first study which assessed predictors for NICU admission in a group of preeclamptic pregnant women including both term and preterm deliveries in a prospective manner. We tried to include all possible confounders reported in the literature in multivariate regression model.

In conclusion, gestational age at delivery and the birth weight are main risk factors for neonatal intensive care unit admission in pregnant women with preeclampsia after adjustment for hypertensive medication, preeclamptic symptoms, regular follow-up, MgSO4 infusion, route of delivery.

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