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Research Article

Comparative Evaluation of Hematology and Biochemistry Before and After Administration of Nifedipine and Isoxsuprine in the Treatment of Preterm Labor.

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ABSTRACT

The safety profile of Nifedipine and Isoxsuprine on preterm diagnosed patients was assessed in this study. A total of 156 patients were included in the study, 78 patients data in each group was utilized for comparing the pre and post administration effects on blood biochemistry and hematology parameters. The dose of Isoxsuprine as an infusion of Inj. Isoxsuprine 40mg in 500ml Ringer lactate at 0.08mg/min, and nifedipine as an initial oral loading dose of 30 mg (10 sublingual and 20 mg oral) and maintenance dose oral dose of 20 mg at every 6 h did not affect the blood biochemistry and hematology of the preterm labor patients and were judged to be clinically non-significant in both the groups except a significant ($p<0.05$) increase in serum urea levels in Isoxsuprine treated patients.

Key Words: Nifedipine, Safety Evaluation, Isoxsuprine, Preterm Labor.

INTRODUCTION

During pregnancy there are many physiological changes, which are considered normal, such as cardiovascular, hematological, metabolic, renal and respiratory changes which are considered necessary and important to balance the physiological and homeostatic mechanisms to ensure the fetus is protected against harmful reactions. Increases in blood sugar, breathing and cardiac output are all required. Levels of progesterone and oestrogens rise continually throughout pregnancy, suppressing the hypothalamic axis and subsequently the menstrual cycle. Pregnancy outcome is influenced by many factors some of which include culture, environmental, socioeconomic status and access to medical care. The hematological profile of pregnant women also has an impact on pregnancy and the outcome of the pregnancy[1-3].

In the past, few if any laboratory tests were performed on pregnant women. There was no laboratory testing routinely associated with pregnancy. In the year 2005, the scope of laboratory testing for pregnant women has increased. Much of the laboratory testing done during pregnancy is not in the realm of the clinical chemistry department[4,5]. Laboratory tests that are offered routinely to pregnant women screen for common problems and usually have guidelines to describe appropriate follow-up. However, when there is additional treatment with drugs to overcome complications, there is always a concern that a pregnant woman and the fetus may get affected. Hence this safety assessment attempted to step through preterm labor patients admitted, analyzing safety effects of a very old drug Isoxsuprine and very recently but rarely used Nifedipine in the treatment of preterm labor with relevance to the effects on blood biochemistry and hematology, before and after administration of either of the drugs as a tocolytic.

METHODS

The study was conducted in Patients above 18 years old with singleton pregnancies and cervical dilatation not more than 4cm and intact membranes who were admitted for preterm labor at CSI Kalyani Multi Specialty hospital at 28 and 36 weeks' gestation were considered eligible for the study[6]. A total of 156 volunteers were included in the study, 78 volunteers data in each group was utilized for comparing the pre and post administration effects on blood biochemistry and hematology parameters irrespective of the successful ness in the tocolytic therapy. The Hospital Ethics Committee approved the study, and written informed consent was obtained from the entire patient and or their legal representative prior to their enrollment in to the study. Written informed consent was obtained from all participants. Procedures followed were in accordance with ICH – GCP (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use), Schedule Y (Drugs and Cosmetics act 1940 India) and the applicable regulatory guidelines. After informed consent was obtained, the patient was assigned to the nifedipine with an initial oral loading dose of 30 mg (10 sublingual and 20 mg oral) and a maintenance oral dose of 20 mg every 6 h. If spontaneous rupture of membranes occurred within 48 hours of treatment, delivery was considered. To enhance fetal lung maturation, all the patients were given head low position and injection dexamethasone 12 mg im 12 hourly for two doses followed by weekly injections up to 36 weeks and

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Table 1: Comparative Biochemical Laboratory parameters before and after Treatment

	Nifedipine (N=78)	Isoxsuprine (N=78)	P Value
	Mean ± SD	Mean ± SD	
Plasma Glucose Before Drug Administration (mg/dL)	93.55±15.67	95.77±17.86	0.20
Plasma Glucose After Drug Administration (mg/dL)	90.16± 23.75	89.86±23.12	0.46
Urea Before Drug Administration (mg/dL)	21.58± 5.35	20.90±6.18	0.23
Urea After Drug Administration (mg/dL)	17.38±5.15	19.28±6.85	0.02
Creatinine Before Drug Administration (mg/dL)	0.82±0.15	0.81±0.16	0.40
Creatinine After Drug Administration (mg/dL)	0.71±0.22	0.72±0.24	0.42
Total cholesterol Before Drug Administration (mg/dL)	187.18±35.02	176.41±35.16	0.02
Total cholesterol After Drug Administration (mg/dL)	174.71±44.81	164.47±44.15	0.07
Bilirubin (Total) Before Drug Administration (mg/dL)	0.66±0.27	0.60±0.20	0.05
Bilirubin (Total) After Drug Administration (mg/dL)	0.54±0.23	0.52±0.21	0.24
Bilirubin (Direct) Before Drug Administration (mg/dL)	0.04±0.00	0.04±0.00	0.15
Bilirubin (Direct) After Drug Administration (mg/dL)	0.04±0.01	0.04±0.01	0.35
Total Protein Before Drug Administration (gm/dL)	57.85±47.26	53.87±41.48	0.29
Total Protein After Drug Administration (gm/dL)	11.58±28.51	14.86±32.83	0.25
Alkaline Phosphatase Before Drug Administration (IU/L)	49.10±37.22	49.19±41.57	0.49
Alkaline Phosphatase After Drug Administration (IU/L)	13.39±14.26	13.74±14.97	0.44
SGOT (AST) Before Drug Administration (U/L)	25.75±11.85	24.72±9.20	0.27
SGOT (AST) After Drug Administration (U/L)	27.43±12.88	25.16±12.93	0.13
SGPT (ALT) Before Drug Administration (U/L)	17.56±15.39	16.29±12.33	0.28
SGPT (ALT) After Drug Administration (U/L)	13.54±16.20	14.82±19.24	0.32
Albumin Before Drug Administration (gm/dL)	5.88±6.69	6.59±8.73	0.28
Albumin After Drug Administration (gm/dL)	2.05±6.04	2.79±9.88	0.28
Globulin Before Drug Administration (gm/dL)	8.43±19.64	8.93±20.74	0.43
Globulin After Drug Administration (gm/dL)	5.72±20.97	6.65±24.16	0.39

Antibiotic prophylaxis was given in the form of erythromycin to patients. Rest and hydration for half an hour was applied as first line management in all cases, Normal saline infusion at a rate of 100-150ml/hr after an initial bolus of 200ml was given for hydration. Blood biochemistry and hematology was done at start (before administration of either isoxsuprine or Nifedipine) and repeated after 24hrs of drug treatment.

The Baseline safety hematological and biochemical parameters were obtained before the start of tocolytic therapy and post study safety hematological and biochemical parameters were obtained after 24 Hrs of tocolytic therapy in both the groups. Hematological parameters included Hemoglobin, RBC, Total Leukocyte count and Platelet count. Biochemical parameters included Plasma Glucose, Blood Urea, Serum Creatinine, Total Cholesterol, Bilirubin (Total), Bilirubin (Direct), SGOT and SGPT. Hematological parameters such as Hemoglobin, RBC, Total Leukocyte count and Platelet count were estimated using SYSMEX XS 800i. Biochemical parameters such as Glucose by GOD-POD method, Blood Urea by UREASE-GLDH (Glutamate Dehydrogenase) /UV Kinetic Method, Serum Creatinine and SGPT by Modified Jaffes method (Initial rate or fixed time method), SGOT by UV Kinetic Modified IFCC without PLP method, Total Cholesterol by CHOD-PAP (Cholesterol Oxidase - Peroxidase) (Enzymatic Photometric method) and Billirubin Total and Billirubin Direct by Jendrassik- Grof Method using SELECTRA-Pro M. In house derived range values were used as reference range values for both hematology and biochemistry laboratory values. Safety Analysis was done for all the subjects in the study so as to facilitate analysis of uniformly paired data. For evaluation of changes versus baseline, both paired t-tests and the Wilcoxon matched- paired signed-ranks tests were applied; usage of both these tests allows the test with the lower (stricter) P value to be chosen if results are different. Analyses of the data were performed with the SPSS statistical package, version 10.0 (SPSS for windows, SPSS Inc., Chicago, IL).

RESULTS AND DISCUSSION

The blood biochemistry means, standard deviations of 78 patients data obtained before administration and after administration of Nifedipine and Isoxsuprine are shown in Table 1 and blood hematology are shown in Table 2.

Blood Biochemistry Results

Plasma blood glucose levels is largely determined by the balance of glucose moving into and leaving the extracellular compartment the normal blood glucose during pregnancy is 95mg/dl, the mean plasma blood glucose before (p= 0.207) and after (p=0.469) administration of Nifedipine and Isoxsuprine did not show any significant changes[7]. Urea or uric acid is the end product of purine metabolism, low urea levels appear to be of no clinical significance, increase in uric acid may be as a result of increased formation of uric acid and decreased excretion, the normal urea levels during pregnancy is 55mg/dl[8]. The mean plasma urea before administration did not find any significant changes (p= 0.233) however there was significant change (P<0.05) after administration of Nifedipine and Isoxsuprine in the urea levels. The increased levels of urea in Isoxsuprine groups

Table 2: Comparative Hematological Laboratory parameters before and after Treatment

	Nifedipine	Isoxsuprine	P Value
	Mean ± SD	Mean ± SD	
Hb (g/dL) Before Administration	12.88±1.50	12.84±1.35	0.44
Hb (g/dL) After Administration	11.75±3.16	11.92±2.77	0.36
RBC ($x10^6$/ µL) Before Administration	4.82±0.46	4.85±0.46	0.37
RBC ($x10^6$/ µL) fter Administration	4.85±0.46	8.66±1.49	0.37
Total Leucocyte count (Cu.mm) ($x10^3$/ µL) Before Administration	8.66±1.49	8.40±1.92	0.17
Total Leucocyte count (Cu.mm) ($x10^3$/ µL) After Administration	7.82±2.47	10.59±22.89	0.35
Neutrophil (%) Before Administration	58.65±7.31	56.40±6.64	0.02
Neutrophil (%) After Administration	10.59±22.89	10.99±22.51	0.46
Lymphocytes (%) Before Administration	31.62±6.63	33.03±6.69	0.10
Lymphocytes (%) After Administration	5.38±11.96	6.73±13.73	0.26
Monocytes (%) Before Administration	5.08±10.08	4.10±1.12	0.20
Monocytes (%) After Administration	0.76±1.65	0.84±1.75	0.38
Eosinophil (%) Before Administration	5.40±4.28	6.08±4.13	0.16
Eosinophil (%)	1.02±2.63	1.00±2.44	0.48
Basophil (%) Before Administration	0.39±0.25	0.39±0.26	0.44
Basophil (%) After Administration	0.11±0.26	0.12±0.28	0.39
Platelet count (lakhs/Cu.mm) & x109/L Before Administration	42.33±94.81	43.08±98.90	0.48
Platelet count (lakhs/Cu.mm) & x109/L After Administration	44.95±101.20	42.74±101.28	0.45
ESR (mm/hour) Before Administration	11.65±7.98	11.32±7.79	0.40
ESR (mm/hour) After Administration	10.81±81.24	10.78±3.92	0.17

may be due to a high protein intake from the diet which is likely to happen as the study groups have been administered with standard diet or the increase should have been caused due to renal disease which also cannot be considered since impaired renal function was an exclusion criteria in the study finally we could conclude that Isoxsuprine drug could have been a chance to increase urea in Isoxsuprine treated group the increase of urea in Isoxsuprine group may be due to the fact that Isoxsuprine gets eliminated through urine hence affecting the renal function. Serum creatinine concentration is largely determined by its rate of production, rate of renal excretion and volume of distribution. The normal range of creatinine in pregnant women is considered to be 0.6 to 1.1 mg/dL. The mean serum creatinine before (p= 0.406) and after (p=0.426) administration of Nifedipine and Isoxsuprine did not show any significant changes[9]. There was significant (P<0.05) change observed in Nifedipine and Isoxsuprine group before administration of either of the drugs in Total cholesterol levels however this does not have any impact if the drugs under the study, moreover the changes observed in the total cholesterol after administration of Nifedipine and Isoxsuprine was not significant(p=0.078).An elevation of serum bilirubin concentrations above 0.05 mg/dl approximately 2.5 times the normal upper limit will reveal itself as jaundice , neither Nifedipine nor Isoxsuprine did increase the serum bilirubin levels after administration during tocolytic treatment, even though there was a significant (p=0.05) decrease observed before administration either Nifedipine or Isoxsuprine, which was considered clinically non-significant. The two transaminases of diagnostic use are aspartate transaminase (AST) and alanine transaminase (ALT) these enzymes are found in many body tissues, with highest concentration being in hepatocytes and muscle cells. Serum AST levels are increased in a variety of disorders including liver disease, crush injuries, severe tissue hypoxia,and pancreatitis. ALT is elevated to a similar extent in the disorders listed which involve the liver. In context of liver disease, increased transaminase activity indicates deranged integrity of hepatocyte necrosis. The data obtained in the current study shows that Nifedipine and Isoxsuprine did not show any significant change in AST or ALT after administration.

Blood Hematology Results

Hematology profile is an important part of the investigation. During pregnancy a woman's need for iron to build more hemoglobin increases. Regular hemoglobin testing is an important part of prenatal care. During the last trimester of pregnancy, a condition known as "physiological anemia of pregnancy" occurs. This normal drop in hemoglobin values results from an increase in the plasma volume[10]. The leukocyte and neutrophil counts, monocyte count, eosinophil count, basophil did not significantly change after the administration of both Nifedipine and Isoxsuprine during preterm labor[11]. However the significant decrease in Neutrophil count before the administration does not have impact in the study. Platelets are formed in the bone marrow. A marked reduction in platelet number may reflect either a depressed synthesis in the bone marrow or destruction of formed platelets. A small platelet count may be seen in pregnancy and following viral infection, however we did not document any fall in the platelet count before and or after administration of either Nifedipine or Isoxsuprine[12]. The erythrocyte sedimentation rate is a measure of the settling rate of red cells in a sample of

anticoagulated blood, over a period of 1 hour in a cylindirical tube the normal value is 10 mm/hr however the normal range raises with age[13]. In a diseased state the raise in ESR is an increased protein level in blood.

CONCLUSION

Laboratory analytes for individuals are subject to several sources of variation, including biological, preanalytical (specimen collection), analytical (bias and imprecision), and postanalytical (reporting of results). Analytical bias is the closeness of an analyte result to the ‘‘true value’’ of the result. Precision is the repeatability of an analyte result if the same sample is tested many times. Biological variation consists of within-person (WP) and between-person (BP) variation[13]. The current study had observed that there was a significant increase in the serum urea levels in post administration of the isoxsuprine however there was no significant increase or decrease in the Hematology or Biochemistry results after administration of Nifedipine. We conclude that a Nifedipine shall be a safe drug in preterm labor considering the safety results obtained in Hematology and biochemistry tests.

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