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SERUM CONCENTRATION OF PYRAZINAMIDE SUSPENSION IN CHILDREN WITH TUBERCULOSIS: A THERAPEUTIC DRUG MONITORING

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ABSTRACT

Rationale. Therapeutic drug monitoring (TDM) is a process of adjusting drug dosages on the basis of serum drug concentrations for the purpose of optimizing drug therapy. This study introduces the use of TDM in the management of mycobacterial infections. Pyrazinamide (PZA) has been marketed as tablet in other countries. It is only in the Philippines wherein pyrazinamide is available both in tablet and suspension forms. No study has been done on pyrazinamide suspension use for the treatment of tuberculosis to this date.

Objectives. To examine the serum concentration of pyrazinamide suspension in children with tuberculosis

Design. Descriptive study

Methods. Thirty pediatric patients who were taking pyrazinamide suspension for at least 1 week as part of chemotherapy for tuberculosis were included in this study. Blood was taken prior to the dose then 2, 4, 8 hours after administration of PZA suspensionfor thefirst 4 patients. Specimens were submitted to the Pharmacology Department Laboratory of the University of the Philippines – College of Medicine and were analyzed using High Performance Liquid Chromatography technique. The samples from the first 4 patients were used to determine the time when the drug reaches its maximum concentration (Tmax). For subsequent patients, 2 determinations were taken at the time when the drug reaches its maximum concentration and trough level.

Results. At at a Tmax of 2 hours, the mean serum concentration of PZA suspension is at 34.6$\pm$ 11.86 ug/ml. The mean serum trough level is 4.55$\pm$ 4.63 ug/ml. There were no significant differences in serum concentration of PZA suspension among 3 brand names of PZA (*p*-value: 0.506).

Conclusion. Mean serum concentration of PZA suspension falls within the established therapeutic range for pyrazinamide. But 2 subjects failed to reach the therapeutic levels. No subject reached toxic levels

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Keywords. Pyrazinamide, antituberculosis, therapeutic drug monitoring, pharmacokinetics, tuberculosis

INTRODUCTION

In the past 4 years, tuberculosis ranks 6th in the leading causes of morbidity in the Philippines. It is also the 5th leading cause of mortality from 1989-1993. Children under 15 years of age represent 1.3 million cases per year and 450,000 deaths per year. Despite the widespread use of BCG vaccine and the availability of effective drugs, TB remains a major health problem. The eradication of TB has proven to be an elusive goal for clinicians and policy-makers. Failure of TB control is not a new phenomenon in our country. Several factors, including irrational antibiotic use, collapse of public health infrastructures, the HIV epidemic, war, famine, increasing inequality and poverty, and prohibitive cost of medicines, have all contributed to the increasing incidence of TB all over the world. In certain situations, drugs provide suboptimal serum concentrations and these are associated with worse treatment outcomes. Recurrence occurs in 2.4-5.5% of cases even when the patient receives directly observed treatment. It is important to maintain high standards of quality assurance, as low quality drugs often penetrate emerging markets, resulting in low cure rates for patients and increased resistance.

Definition of Terms

1. Therapeutic drug monitoring (TDM) – is the process of using serum drug concentrations to optimize drug therapy. TDM is useful when serum concentrations show a better correlation with the therapeutic effects or the incidence of adverse effects than does the size alone. TDM requires the accurate timing of doses and blood collection and the avoidance of assay interferences.

the said parameters were the ones found to be statistically significant. The difference in the sensitivity of hematological values to other studies could be due to wide range of the subjects and some degree of observer variability in reporting the peripheral smear.

CONCLUSION

Neonatal sepsis, especially in its early stages, may be difficult to diagnose because of its nonspecific clinical symptoms. Because the prognosis for sepsis largely depends on early identification and treatment, these neonates are subjected to extensive diagnostic evaluation and empiric treatment.

The usefulness of a scoring system based on the clinical manifestations of the neonate and mother supported by their hematological parameters can provide information in determining the probability of sepsis in neonates. Since this scoring system is highly sensitive and specific for neonatal sepsis, it could also serve as the basis for a more rational approach to antibiotic use. A significant decrease in the use of antibiotics may prevent the emergence of resistant organisms, decrease the chance of side effects and minimize cost.

RECOMMENDATIONS

It is recommended that more subjects will be included in future studies wherein there will be a control group composed of healthy, asymptomatic neonates and a test group composed of neonates with probable sepsis or proven sepsis. The group can also be divided into full term or preterm neonates to determine differences in their hematological characteristics. It also suggested that one interpreter of the laboratory results be assigned to decrease the observer variability.

REFERENCES

1. Manucha V, Rusia U, Sikka M, Faridi MMA, Madan N. Utility of hematological parameters and C-reactive protein in the detection of neonatal sepsis. Journal of Pediatrics and Child Health. 2002; 38: 459-464.
2. Baley J, Goldfarb J, Neonatal Infections. Care of the high risk neonate, 4th edition. MH. MH Klaus and AA Fanaroff: editors. Philadelphia: WB Saunders Company, 1993.
3. David E., Tan CT, Que SP., Cruz NGS. Determining the criteris for early discontinuation of antibiotic therapy in suspected neonatal sepsis. Philippine Journal of Microbial Infectious Diseases. 1980; 9 (2): 145-155.
4. Annual Reports of the Section of Neonatology of the Department of Pediatrics UP-PGH Medical Center. 2000-2002.
5. Bellig L, Ohning B. Neonatal Sepsis. EMedicine Journal Pediatrics/Neonatology. 2003; 4(1). 6. Thilo EH, Rosenberg AA. Infections of the Newborn. Current Pediatric Diagnosis and Treatment, 14th edition. Hay WW, Hayward AR, Levin MJ, Sondheimer JM: editors. New Jersey: Appleton and Lange, 1999.
7. Fowlie PW, Schimdt B. Diagnostic tests for bacterial infection from birth to 90 days- a systematic review. Archives of the Diseases in Child Fetal Neonatal Edition. 1998; 79: 92-98.
8. Kite P, Millar MR, Gorham P, Congdon P. Comparison of five tests used in diagnosis of neonatal bacteremia. Archives of Disease in Childhood. 1988, 63: 639-643.
9. Da Silva O, Ahisson A, Kenyon C. Accuracy of leukocyte indices and C-reactive protein for the diagnosis of neonatal sepsis: a critical review. Pediatric Infectious Diseases Journal. 1995; 14: 362-366.
10. Philip AG. Decreased use of antibiotics using a neonatal sepsis screening technique. The Journal of Pediatrics. 1981, 98(5): 795-799.
11. Zipursky A, Palko RT, Milner MIS, and Akenzua MB. The Hematology of Bacterial Infections in Premature Infants. Pediatrics. 1976, 57(6): 839-853.
12. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. The Journal of Pediatrics. 1979, 95(1): 89-98.
13. Cunningham FG, Grant N. Maternal Adaptations to Pregnancy. Williams Obstetrics, 21st edition. New York: Mc Graw Hill Medical Publishing Division. 2001.
14. Nelson DA, Morris MW. Basic Examination of Blood. Clinical Diagnosis and Management, 18th edition. Henry JB: editors Philadelphia: W.B. Saunders Company. 1991.
15. Anwer S, Mustafa S. Rapid Identification of Neonatal Sepsis. Journal of Pakistan Medical Association. 2000; 50(3).
16. Limjoco-Sarte L, Gonzales RM. Septicemia in Filipino Infants and Children: Analysis of 724 Bacteriologicallly Proven Cases in an Urban Hospital. Philippine Journal of Pediatrics. 1981; 30(6): 190-198.
17. Rodwell RL, Tudehope DA. Early diagnosis of neonatal sepsis using a hematologic scoring sytem. The Journal of Pediatrics. 1988; 112(5): 761-767.
18. Akenzua GI, Hui YT, Milner R, Zipursky A. Neutrophil and Band counts in the Diagnosis of Neonatal Infections. Pediatrics. 1974; 54(1): 38-42.
19. Engle WD, Rosenfeld CR. Neutropenia in high risk neonates. The Journal of Pediatrics. 1984; 105(6): 982-986.

manifested most commonly on the first day of life, with majority of cases at less than 12 hours.[6] This was evident in this study wherein there were 77 out of the 100 neonates (77%) presented with respiratory problems. Other clinical signs of bacteremia include unexplained low Apgar scores, poor perfusion, hypotension, bradycardia, and unstable temperature.

Because of the low positivity of blood culture, its inavailability in some peripheral health centers and the time allotted for the result to be obtained, the need for other tests in diagnosing neonatal septicemia is warranted.[1]

The complete blood count with differential is widely used, either singly or in conjunction with other test or clinical findings, as a diagnostic tool for neonatal sepsis. [17]

The criteria of Manroe with 2 of 3 indices (total PMN count, immature PMN count, and I/T ratio) abnormal were the most reliable of the published criteria evaluated and would have identified all infants with sepsis and all infants with probable sepsis.[12,17]

In this study, there were more hematological parameters of the neonates studied. These were total leukocyte count, total neutrophil count, immature cells, immature to total neutrophil cells (I/T) ratio, immature to mature cells (I/M) ratio, platelet count and toxic granulation. Nucleated red blood cells, lymphocytes and absolute neutrophil count were also included because there were no studies done yet in determining its association with sepsis. Moreover, maternal infection was noted to be one of the major risk factors in early neonatal sepsis which could be documented by a complete blood count. Thus, the maternal hematological parameters, consisting of total leukocyte count, total neutrophilic count, lymphocytes and platelet count, were also used as indices in predicting neonatal sepsis.
In the neonatal hematological parameter, only the platelet count was significant with p value of 0.02.

Thrombocytopenia was seen frequently in sepsis proven group. This could result from increased platelet destruction, sequestration secondary to infections, failure in platelet production due to decreased number of megarkaryocytes or damaging effects of endotoxin on the platelets.[11]

Total leukocyte count, total neutrophilic count and immature cells showed no significant association with sepsis. In a study by Akenzua, it was stated that total neutrophil count was of limited value for the diagnosis of infection since elevation is often late and inconsistent. In addition, newborn infants with proven bacterial infection had normal neutrophil count but the bands increased beyond the normal range.[18] In another study, although neutropenia in the newborn is most often secondary to infection, there are many causes of neutropenia including isoimmune neutropenia, congenital neutropenia, and neutropenia due to inborn error of metabolism.[19] Lastly, neutrophilia in the absence of an increase in band may occur in patients with no evidence of infection, presumably the result stress or other non specific causes. Therefore, neutrophilia itself is not a reliable or sensitive test of infection.[11]

Neutrophil ratios were often abnormal during neonatal sepsis. However, this was not evident in this study possibly because of the variation in interpretation of peripheral smears by different observers.

Toxic granules also showed no significant difference in this study. The presence of toxic granules represents the production of unusual neutrophils during the stress leucopoiesis and infection. It is invariably present during sepsis, a change never seen in healthy newborn infants but are not always increased in infection. [11] The other parameters, namely: nucleated red blood cells, lymphocytes and absolute neutrophilic count, were not statistically significant.

The maternal hematological parameter which showed significant correlation between sepsis was total leukocyte count with a negative predictive value of 97.1%. The leukocyte count usually ranges from 5,000 to 12,000 x 10^9/L. During labor and the early puerperium, it may be markedly elevated. The cause is not known but probably represents the reappearance in the circulation of leukocytes previously shunted out of the active circulation. During pregnancy, there is neutrophilia that consists of mature forms.[13]

In this study, there were 3 parameters, namely: preterm neonates, neonatal platelet count of $\leq$150 x 10^9/L, and maternal total leukocyte count of > 12,000 x 10^9/L that were statistically significant. Based on these factors, a scoring system was formulated which could be used in determining the presence of sepsis. The presence of one factor corresponded to a score of 1 which indicated a positive predictive value of 11% and a score of 2 indicated 30% positive predictive value. The probability of getting a positive blood culture increases with an increasing score. The highest score was 3 with 100% sensitivity and 91.3% specificity for predicting neonatal sepsis.

It could be noted that in this study, there were different parameters used for predicting sepsis compared to other hematological scoring sytem.[12] This was because

Correlation of neonatal and maternal factors with neonatl sepsis

The factors which showed statistical significance were preterm neonates, neonatal platelet count and maternal total leukocyte count. In table 5, the odds ratio of having a positive blood culture result was 3 times (OR = 2.92) higher for preterm as compared to full term neonates. The odds ratio for neonates with low platelet count was 5 times (OR = 4.74) higher than the neonates whose platelet count was within normal range. Lastly, for neonates whose maternal total leukocyte count (TLC) was >12, the odds ratio was 11 times higher for neonatal sepsis as compared to patients whose maternal TLC was ≤12. Among these factors, the maternal total leukocyte count had the highest sensitivity of 94.1% and negative predictive values of 97.1% (Table 6).

Table 5: Factors Associated with Neonatal Sepsis

Factors	OR	95% CI	p value
Preterm	2.92	0.88 – 9.98	< 0.05
Neonatal Platelet count (≤150)	4.74	1.16 – 19.65	< 0.05
Maternal TLC (>12)	11.1	1.42 – 87.73	< 0.01

Table 6: Sensitivity, Specificity of Factors Associated with Neonatal Sepsis

Factors	Sensitivity	Specificity	PPV	NPV
Preterm	64.7	60.2	25.0	89.3
Neonatal Platelet count (≤150)	35.3	89.2	40.0	87.1
Maternal TLC (>12)	94.1	41.0	24.6	97.1

A scoring system was devised based on the significant factors that were obtained in this study. There is a significant difference in the median scores of the patients with positive blood culture and negative blood culture. Higher median scores were noted among the neonates with positive blood culture (Table 7).

Table 7: Scoring

Scores	Bld CS (+)(n=17)	Bld CS (-)(n=83)	Total
0	0 (0%)	21 (100%)	21
1	5 (11%)	39 (89%)	44
2	9 (30%)	21 (70%)	30
3	3 (60%)	2 (40%)	5

p <0.001 (S)

Since the median scores were significantly different, each score was then computed for its individual accuracy of determining sepsis. A score of 3 was both highly sensitive and specific for neonatal sepsis. The chance of getting a positive blood culture given all the 3 factors was 100%. While, if the factor were absent, the chance of a negative blood culture was 91.3% (Table 8).

Table 8: Sensitivity, Specificity of Score Associated with Neonatal Sepsis

Scores	Sensitivity	Specificity	PPV	NPV
1	100	35.0	11.4	100
2	100	50.0	30.0	100
3	100	91.3	60.0	100

DISCUSSION

A high index of suspicion is important in the diagnosis and treatment of neonatal infection because it is hampered by vague, nonspecific or nonexistent clinical manifestation. Thus, it is difficult to establish a diagnosis based on clinical picture alone. However, it is imperative that treatment is instituted early because of the high mortality associated with the neonatal infection.

In this study, there was 17% culture proven neonates with sepsis which were predominantly preterm (64.7%) and males (70.6%). This was possibly due to impaired defense mechanisms and low immunoglobulin G levels in males and low birth weight neonates.[15] In addition, newborns particularly the preterm, have less effective phagocytosis and chemotactic activity. Therefore, rapid invasion of offending organism occur very fast. They also have relative immunoglobulin M deficiency rendering them more vulnerable to gram negative infections.[16]

Infections occurring at less than 72 hours of age usually are caused by bacteria acquired in utero or during delivery, whereas infection after that time most likely have been acquired after birth.[13] Thus, it is essential to know the maternal illnesses which can predispose to neonatal sepsis. These are prolonged rupture of membranes, foul smelling amniotic fluid, maternal fever or other symptoms suggestive of infection, unexplained fetal distress and previous septic infant. It was noted that there were 76.5% neonates with culture proven sepsis who had maternal history of infection. However, the result showed no significant difference which could be attributed to prior antibiotic intake of the mothers during the time of illness.

The most common presenting symptom in the early onset of sepsis is respiratory distress. It is

Table 3: Association of the Neonatal Hematological Parameters with Neonatal Sepsis (cont'd)

Hematological parameters	Blood CS (+) (n=17)	Blood CS (-) (n=83)	Total	p value
I/T Mean +/- SD Range Median	0.108 +/ - 0.197 0 – 0.640 0	0.063 +/ -0.131 0 –0.784 2		0.05 (NS) (t-test)
I/T >0.16 ≤0.16 square	4(23.5%) 10 (58.8%)	13 (15.7%) 44 (53.0%)	17 83	>0.05 (NS) (Fisher-test)
I/M Mean +/- SD Range Median	0.216+/ -0.473 0-1.790 0	0.074 +/ -0.159 0 – 0.750 0		0.05 (NS) (t-test)
I/M > 0.3 ≤ 0.3	3 (17.6%) 14 (82.4%)	7 (8.4%) 76 (91.6%)	10 90	>0.05 (NS) (Fisher test)
ANC Mean +/- SD Range Median	7164 +/ -7291 1620-32500 5044	9788 +/ -6745 582 -34850 8959		0.05 (NS) (t-test)
Platelet count (x10⁹/L) Mean+/-SD Range Median	200.5+/ -108.8 54-375 203.50	243.4 +/ -85.4 55-456 243.00		0.05 (NS) (test)
Platelet count (x10⁹/L) Mean+/-SD ≤ 150 > 150	6 (35.3%) 6 (35.3%) 11 (64.7%)	9 (10.8%) 55-456 74 (89.2%)	15 85	0.02 (S) (Fisher test)
Toxic granules (+) (-)	6(35.3% 11 (64.7%)	30 (36.1%) 53 (63.9%)	36 64	>0.05 (NS) (chi-square test)
Toxic granules ≥ 3 + < 3 Normal	0 (0%) 17 (100%)	0 (0%) 83 (100%)	0 100	NA

Maternal hematological parameters and neonatal sepsis

The obtained results of the maternal total leukocyte count showed no significant difference but when compared to the reference value for pregnant women[12], the results were significant. There were 94.1% mothers who had leukocytosis in the confirmed sepsis group with p value of 0.006. The other hematological parameters namely segmenter, lymphocyte and platelet count had no statistical significance (Table 4).

Table 4: Association of the Maternal Hematological parameters with Neonatal Sepsis

Maternal parameters	Blood CS(+) (n=17)	Blood CS(-) (n=83)	Total	*p*-value
WBC (x10⁹/L) Mean +/- SD Range Median	15.47+/-3.61 9.3–23.19 15.30	14.29 +/- 5.18 5.9 – 30.4 13.20		> 0.05 (NS) (t-test)
WBC (x10⁹/L) >12 ≤12	16 (94.1%) 1(5.9%)	49 (59.0%) 34 (41.0%)	65 35	0.006 (S) (chi-square test)
Segmenter (x10⁹/L) Mean +/- SD Range Median	12.53+/- 3.89 6.70–21.24 12.71	11.01 +/-4.76 7.87 – 25.84 10.19		> 0.05 (NS) (t-test)
Segmenter (x10⁹/L) 1.8 – 7 <1.8 – >7	1 (5.9%) 16 (94.1%)	1 (1.2%) 82 (98.8%)	2 98	> 0.05 (NS) (Fisher-test)
Lymphocyte (x10⁹/L) Mean +/- SD Range Median	1.85 +/- 0.9 0.88–3.84 1.71	2.18 +/- 1.13 2.33 – 7.44 1.97		> 0.05 (NS) (t-test)
Lymphocyte (x10⁹/L) 1 – 4.8 < 1 - > 4.8	16 (94.1%) 1 (5.9%)	75 (90.4%) 8 (9.6%)		> 0.05 (NS) (Fisher-test)
Platelet count (x10⁹/L) Mean +/- SD Range Median	335.7+/- 97.3 135 – 467 336	292.5 +/- 101.5 69 – 677 277		> 0.05 (NS) (t-test)
Platelet count (x10⁹/L) 150 - 400 < 150 - > 400	0 (0%) 17 (100%)	1 (1.2%) 82 (98.8%)	1 99	> 0.05 (NS) (Fisher-test)

There were 13 out of the 67 mothers who had illnesses during pregnancy with culture proven sepsis as shown in Table 2. The maternal illnesses were upper respiratory tract infection, urinary tract infection, and premature rupture of membrane.

It was also noted that there were no significant difference in the Apgar scores, neonatal symptoms and maternal illnesses.

Table 2: Association of the neonatal clinical symptoms and maternal symptoms with Neonatal Sepsis

Clinical profile	Blood CS (+) (n=17)	Blood CS (-) (n=83)	Total	p value
Apgar score at 1-min 1 – 3 4 – 6 7 – 9 Mean	 4 (23.5%) 4 (23.5%) 9 (52.9%) 6	 14 (16.9%) 18 (21.7%) 51 (61.4%)%6 1 (1.2%)	 18 22 60	 > 0.05 (NS)
Apgar score at 5-mins 3 4 – 6 7 – 9 10 Mean	 1 (5.9%) 4 (23.5%) 12 (70.6%) 0 8	 9 (10.8%) 71 (85.5%) 2 (2.4%) 8 18	 2 13 83 2	 > 0.05 (NS)
Neonatal Symptoms Rule out Sepsis HMD TTN Pneumonia MAS	 5 (29.4%) 6 (35.3%) 1 (5.9%) 3 (17.6%) 2 (11.8%)	 (21.7%)14 (16.9%)20 (24.1%)17 (20.4%)14 (16.9%)	 23 20 21 20 16	 > 0.05 (NS) (chi-square test)
Maternal Symptoms (+) (-)	 13 (76.5%) 4 (23.5%)	 54 (65.0%)29 (35.0%)	 67 33	 > 0.05 (NS) (chi-square test)

Neonatal hematological parameters and neonatal sepsis

The details of the neonatal hematological parameters are shown in Table 3. The mean total leukocyte count of the neonates with sepsis was significantly lower than those without sepsis (p=0.03). However, when compared to the reference values, there was no significant difference. It could be noted that there were 14 neonates with sepsis (82.4%) whose total leukocyte count were within the normal range. The nucleated red blood cells, total neutrophil count or segmenters, lymphocytes, immature cells, I/T ratio, I/M ratio, absolute neutrophil count and toxic granules were not statistically significant. It was only the platelet count which was significant (p=0.02) when compared to the reference value.

Table 3: Association of the Neonatal Hematological Parameters with Neonatal Sepsis

Hematological parameters	Blood CS (+) (n=17)	Blood CS (-) (n=83)	Total	p value
NRBC Mean +/- SD Range Median	 25.24 +/ - 44.81 0 – 146 2	 5.46 +/ - 13.54 0 – 85 2	 	 0.05 (NS) (t-test)
NRBC 0 >0	 7(41.2%) 10 (58.8%)	 39 (47.0%) 44 (53.0%)	 46 54	 >0.05 (NS) (chi-square
TLC (x10^9/L) Mean +/- SD Range Median	 12.14 +/- 8.68 4.50-41.90 10.2	 16.66 +/ -7.78 1.70 – 41.00 15.6	 	 0.03 (S)
TLC (x10^9/L) ≤ 5 or ≥25 Normal	 3 (17.6%) 4.50-41.90 14(82.4%)	 13 (15.7%) 70 (8 4.03 15.6	 16 84	 >0.05 (NS) (Fisher test)
TLC (x10^9/L) Mean +/- SD Range Median	 6.29 +/- 7.54 1.02-32.85 3.50	 9.17 +/ -6.34 0.48-28.56 8.10	 	 0.05 (NS) (t-test)
TNC(x10^9/L) <0.78 or 1.45 Normal	16 (94.1%) 1 (5.9%)	81 (97.6%) 2 (2.4%)	97 3	>0.05 (NS) (Fisher test)
Lymphocytes (x10^9/L) Mean+/-SD Range Median	 4.17+/-2.75 1.08-12.32 4.04	 5.60+/-3.17 0.18-16.71 4.85	 	 0.05 (NS) (test)
Immature Mean +/- SD Range Median	 0.64 +/ - 1.26 0 – 4.45 0	 0.52 +/ - 1.22 0 – 6.97 0	 	 > 0.05 (NS) (t-test)
Immature<0.05 or >1.45 Normal	 16 (94.1%) 1 (5.9%)	 73 (88%) 10 (12%)	 89 11	 > 0.05 (NS) (Fisher test)

venous or arterial puncture within 24 hours of admission before initiation of antibiotic therapy.

A 0.5-1 ml of blood sample was anticoagulated with ethylene diamine tetra acetic acid. The total leukocyte count and platelet count were measured on a Coulter STKS. White blood cells were corrected for nucleated red blood cells. Peripheral blood smears were drawn on clean slides and stained by Wright's stain. A differential leukocyte count was done to obtain the total neutrophil count (TNC), immature neutrophil count (IM), including bands and stabs; and mature neutrophil count (M). Neutrophils were classified as band forms when there were no nuclear segmentation or when the width of the nucleus at any constriction was not less than one third the width at its widest portion. Band forms together with less mature cell form were classified as immature polymorphonuclear (PMN) leukocytes. Using these values, I/M and I/T ratios were computed. One hundred neutrophils were further examined for degenerative changes such as toxic granulation, Dohle bodies, and vacuolization. Toxic granulation was graded as 0 or (-) which indicated normal granulation or no toxic granules seen, (+) slight, (++) approximately 50% of neutrophils contained dark granules, (+++) very high granulation in most cells, and (++++) gross toxic granulation with the nucleus obscured by toxic granules.[11]

One milliliter of blood was inoculated aseptically into 20ml of brain heart infusion broth for culture and sensitivity. Newborn infants with positive blood cultures were considered to have proven sepsis while the others were still considered as clinically suspected of infection.

The clinical manifestations and hematological parameters were compared, individually and in combination, with the blood culture result.

Statistical analysis

Data were analyzed by using T-test to compare two groups with numerical data, Chi-square test to compare or associate nominal data and Fisher Exact test when the expected frequencies are less than 5. A level of 0.05 was considered statistically significant. The reference values of the neonatal hematological parameters of Manroe, et al were used as the standard values.[12] The maternal reference values used were taken from the values for pregnancy.[13-14] The results that were statistically significant in this study were used to design a hematologic scoring system that will predict the probability of sepsis.

RESULTS

Neonatal profile and neonatal sepsis

There were 17 neonates who had culture proven sepsis which had a prevalence of 17%. Eleven of the 17 neonates were preterm (64.7%) and 6 were full term neonates (35.3%). There was a significant correlation between preterm and positive blood culture with p value of 0.047. The neonatal profile showed that 12 males (70.6%), 11 appropriate for gestational age (64.7%) with mean birth weight of 2000 grams and 11 infants delivered via caesarian section (64.7%) had culture proven sepsis. However, these data were not significant (Table 1).

Table 1: Association of neonatal profile with neonatal sepsis

Patient's Profile	Blood CS (+) (n=17)	Blood CS (-) (n=83)	Total	*p* value
Pre-term	11 (64.7%)	32 (38.6%)	43	0.047 (S)
Full-term	6 (35.3%)	51 (61.4%)	57	(chi-square test)
Sex				
Male	12 (70.6%)	50 (60.2%)	62	> 0.05 (NS)
Female	5 (29.4%)	33 (39.8%)	38	(chi-square test)
Weight(gm)				
Mean +/- SD	2012+/-920.7	2289+/-768.6		> 0.05 (NS)
Range	1000 – 3800	1000 – 3900		(t-test)
Weight for pediatric age				
AGA	11 (64.7%)	63 (75.9%)	74	> 0.05 (NS)
LGA	2 (11.8%)	1 (1.2%)	3	> 0.05 (NS)
SGA	4 (23.5%)	19 (22.9%)	23	> 0.05 (NS) (Fisher test)
Manner of Delivery				
LSCS	11 (64.7%)	41 (49.4%)	52	
OFE	0 (0%)	7 (8.4%)	7	> 0.05 (NS)
SVD	6 (35.3%)	35 (42.2%)	41	(chi-square test)

The bacterial species isolated showed that 14 of the 17 (82.3%) blood culture isolates were Alkaligenes faecalis followed by Acinetobacter (n=1), Diphteroides (n=1) and Staphylococcus epidermidis (n=1).

Clinical profile and neonatal sepsis

Majority of the clinical manifestations of the newborns who were suspected with sepsis had concomitant respiratory diseases (n=77) and only 23 patients had primary impression of sepsis clinically or based on the maternal history of infection. Among the neonates with culture proven sepsis, there were 12 neonates who had respiratory problems (70.6%).

However, due to the high cost of antibiotics, inavailability of blood cultures in some community hospitals, and the time it takes for the blood culture result to come out, several studies have examined the laboratory findings associated with sepsis. There is a lack of consensus on the essential test that would identify neonates with acute infection. In a systematic review to determine the value of diagnostic tests for bacterial infection in early life, it was reported that the accuracy of tests varies enormously and the tests are of limited value in the diagnosis of infection.[7] In another study, a combination of hematological and biochemical tests (eg. acridine orange leukocyte cytospin test, nitroblue tetrazolium and C-reactive protein) may provide a more rapid and accurate diagnosis of bacteremia than conventional microbiological methods.[8] In recent years, various investigators have evaluated some highly sensitive and specific inflammatory markers (eg. C-reactive protein, interleukin-6, interleukin-8, plasma elastase) to diagnose neonatal sepsis and shock. Although these markers are sensitive and specific, they require sophisticated and expensive kits and are therefore impractical for routine clinical work-up in a community health delivery systems, particularly in developing countries.[1]

The use of hematological parameters for determining sepsis was evaluated in different studies. There was significant heterogenicity across these studies.[9] The possible sources were population, age, subjects, methodological quality, different leukocyte indices, different cut-offs and interpretation of test results by different laboratory observers. However, these parameters remain to be rapid, economical, feasible, practically possible in all laboratories and most especially, these hematological parameters can be used as a tool in screening neonates with sepsis[1] which in turn may decrease the antibiotic usage.[10]

GENERAL OBJECTIVE

This study is designed to evaluate the neonatal and maternal clinical manifestations and their hematological parameters, individually and in combination, as parameters which can be used to formulate a scoring system in predicting the probability of neonatal sepsis.

SPECIFIC OBJECTIVES

1. To provide a rapid identification of sepsis based on complete blood count and peripheral blood smear in correlation with clinical symptoms
2. To compare neonates who are more prone to infection based on gestational age, weight, sex and manner of delivery
3. To determine whether the newborn and maternal symptoms correlate well with neonatal sepsis
4. To determine which of the newborn hematological parameters, namely: the white blood count (WBC) or total leukocyte count (TLC), total neutrophil count (TNC), lymphocytes, immature cells, immature to total neutrophil cells (I/T) ratio, immature to mature cells (I/M) ratio, absolute neutrophil count, nucleated red blood cells (NRBC), platelet count and toxic granulation, are significant in predicting sepsis
4. To determine whether the maternal white blood count, different count, and platelet count are also significant in predicting sepsis

STUDY DESIGN

This is a cross-sectional study conducted at the Neonatal Intensive Care Unit of a tertiary care teaching hospital.

METHODS

Subjects

The study consisted of 100 neonates admitted at Neonatal Intensive Care Unit (NICU) at the Philippine General Hospital from July to September 2003 who were clinically suspected of sepsis at birth and within 24 hours of life or had maternal history of infection.

Inclusion Criteria:

Neonates with respiratory distress syndrome, cyanosis, apnea, transient tachypnea, meconium aspiration syndrome, pneumonia, low Apgar score, birth asphyxia, lethargy, temperature instability, and hypoglycemia.

Neonates with maternal history of infection such as upper respiratory tract infection, pneumonia, urinary tract infection, vaginitis, premature rupture of membrane, chorioamnionitis, with or without antibiotic intake during pregnancy.

Newborn with gestational age of 30 weeks and above by pediatric aging and with a weight of more than or equal to 1000 grams.

Study Procedure

Each neonate was examined by a pediatric resident rotating in NICU or neonatology fellow who recorded the signs and symptoms of the neonate, predisposing perinatal factors and the clinical assessment of the neonate.

Initial tests performed were complete blood count, peripheral smear and blood culture. Blood samples (2 ml) were collected from the umbilical cord, peripheral

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CLINICAL CORRELATION OF NEONATAL AND MATERNAL HEMATOLOGICAL PARAMETERS AS PREDICTORS OF NEONATAL SEPSIS

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ABSTRACT

Objective: To evaluate the neonatal and maternal clinical manifestations and their hematological parameters, individually and in combination, as parameters which can be used to formulate a scoring system in determining neonatal sepsis.

Design: A cross-sectional study conducted at the Neonatal Intensive Care Unit of a tertiary care teaching hospital.

Methods: The study consisted of 100 neonates admitted at Neonatal Intensive Care Unit at the UP-PGH Medical Center who were clinically suspected of sepsis at birth and within 24 hours of life. A perinatal history, clinical profile, symptoms and laboratory data were recorded in each case. The neonatal hematological parameters included were total leukocyte count, total neutrophil count, lymphocytes, immature cells, immature to total leukocyte ratio, immature to mature cells ratio, nucleated red blood cells, lymphocytes, absolute neutrophil count, platelet count, and toxic granules. The maternal hematological parameters consisted of total leukocyte count, total neutrophil count, lymphocytes and platelet count. These parameters were evaluated based on the standard reference values. A blood culture was the standard indicator for proven sepsis.

Results: There were 17 out of 100 neonates (17%) who had culture proven sepsis and they were predominantly preterm. Among the different parameters, the preterm infants, neonatal platelet count and maternal total leukocyte count were significantly associated with neonatal sepsis with *p* value of 0.047, 0.02, and 0.006 respectively. Based on these factors, a scoring system was devised to predict the probability of sepsis. A score of 3 had a 100% sensitivity and 91.3% specificity.

Conclusion: A scoring system for predicting neonatal sepsis could be obtained by correlating the clinical manifestations of the neonate and the mother together with their hematological parameters.

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Keywords: Neonatal sepsis, hematological parameters, scoring system, newborn, perinatal infection

INTRODUCTION

Sepsis neonatorum is used to describe the systemic response to infection in newborn infants. It continues to be the major cause of morbidity and mortality in the newborn.[1] Neonatal sepsis occurs in 1 to 8 cases of all live births.[2] In the Philippines, the incidence is estimated between 4 to 9 cases per 1000 live births.[3] In the Neonatal Intensive Care Unit of the University of the Philippines – Philippine General Hospital, it is estimated between 2 to 7 cases per 1000 live births with an average sepsis rate of 7%.[4]

Neonatal sepsis is categorized as early or late onset. Eighty-five percent of newborns with early onset of infection present within 24 hours, 5% present at 24-48 hours, and a smaller percentage of patients present between 48 hours and 6 days of life.[5] The susceptibility of the newborn is related to immaturity of both the cellular and humoral immune systems at birth. This feature is particularly evident in preterm neonate. Early-onset sepsis syndrome is also associated with acquisition of microorganisms from the mother through blood-borne transplacental infection of the fetus, ascending infection, and infection upon passage through an infected birth canal or exposure to infected blood at delivery.[6] Late-onset sepsis syndrome occurs at 7-90 days of life and is acquired from the care-giving environment.

The early signs of sepsis in the newborn are nonspecific. Therefore, many newborns undergo diagnostic studies and the initiation of treatment before the diagnosis has been determined. The definitive diagnosis of septicemia is made by a positive blood culture.[1] The incidence of culture proven sepsis is approximately 2 in 1000 live births. Of the 7-13% of neonates who are evaluated for sepsis, only 3-8% have culture proven sepsis. The mortality rate of untreated sepsis can be as high as 50%.[5] Thus, most clinicians believe that the hazard of untreated sepsis is too great to wait for confirmation by positive cultures. They initiate treatment while awaiting culture results.

16. Vost, Longstaff.. Infection control and related issues in intravascular therapy. Br J Nurs 1997 Aug 14-Sep 10; 6 (15); 846-8, 850, 852 passim
17. Campbell, Carrington. Peripheral i.v. cannula dressings: advantages and disadvantages. Br J Nurs 1999 Nov 25-Dec 8 ; 8(21): 1420-2
18. Garland, Nelson, Cheah, Hennes, Johnson. Infectious complications during peripheral intravenous therapy with Teflon catheters: a prospective study. Pediatr Infect Dis J 1987 Oct; 6 (10): 918-21
19. Harris, Alford, Dan, Savage. Bacteremia related to IV cannulation: variability of underlying venous infection. South Med J 1980 Jun; 73(6):719-22
20. Hershey, Tomford, McLaren, Porter, Cohen. The natural history of intravenous catheter-associated phlebitis. Arch Intern Med 1984 Jul; 144(7): 1373-5
21. Hoffmann, Weber, Samsa, Rutala. Transparent polyurethane film as an intravenous catheter dressing. A meta-analysis of the infection risks. JAMA 1992 Apr 15; 267(15):2072-6
22. Hoffmann, Western, Kaiser, Wenzel, Groschel. Bacterial colonization and phlebitis-associated risk with transparent polyurethane film for peripheral intravenous site dressings. Am J Infect Control 1988 Jun; 16(3): 101-6
23. McKee, Shell, Warren, Campbell. Complications of intravenous therapy: a randomized prospective study – Vialon vs. Teflon. J Intraven Nurs 1989 Sep-Oct; 12(5): 288-95
24. Meylan. Increased risk of bacterial colonization of intravenous catheters covered with transparent adhesive polyurethane bandages, compared to classical gauze bandages. Schweiz Med Wocheenschr 1987 Dec 12; 117
25. Monreal, Quilez, Rey-Joly, Rodriguez, Sopena, Neira, Roca. Infusion phlebitis in patients with acute pneumonia. Chest 1999; 115: 1576-80
26. Nelson, Garland. The natural history of Teflon catheter-associated phlebitis in children. Am J Dis Child 1987 Oct; 141 (10): 1090-2
27. Parras, Ena, Bouza,Guerrero, Moreno, Galvez, Cercenado. Impact of an educational program for the prevention of colonization of intravascular catheters. Infect Control Hosp Epidemiol 1994 Apr; 15 (4 Pt 1): 239-42.
28. Tomford, Hershey, McLaren, Porte, Cohen. Intravenous therapy team and peripheral venous catheterassociate complications. A prospective controlled study. Arch Intern Med 1984 Jun; 1444(6): 1191-4
29. VandenBosch, Cooch, Treston-Aurand. Research utilization: adhesive bandage dressing regimen for peripheral venous catheters.Am J Infect Control 1997 Dec;25(6): 513-9

Since IV cannula is sometimes used several times in an insertion, the number of times the cannula has been used before a successful cannulation has been recorded and analyzed as a risk factor of phlebitis. Although majority of the insertion has been successful on 1st attempt, 14% (7/51) has developed phlebitis while 23%, (3/13), 50% (1/2) and 50%(1/2) has developed phlebitis when the cannula has been reinserted twice, thrice and four times respectively. It is therefore recommended that the IV cannula be used only once and be discarded if attempt is unsuccessful. The cost of IV cannula will however make this suggestion impractical.

These results lead to the question of whether there is a direct relationship between difficulty of insertion as evaluated subjectively by those performing the IV cannulation and by the number of attempts before a successful cannulation has been made. A similar study with such an objective is therefore recommended.

The type of infusate such as irritant IV medication is a significant factor in the development of phlebitis. Among subjects who developed phlebitis, some of the drugs that has been infused and recognized to be often implicated in the development of phlebitis has been IV fluids with KCl and Ca gluconate incorporation and blood products packe RBC and platelet concentrate. There is however particular classification of infusate as to their abiltity and degree to irritate the veins and cause phlebitis. The application of topical mupirocin may not decrease the incidence of chemical phlebitis or those caused by irritant infusate in contrast to those with infectious etiology although both factors may co-exist in the development of phlebitis.

The potential of topical mupirocin in decreasing the incidence of phlebitis therefore needs further confirmation. The amount of ointment used per cannulation is so small that it will not greatly increase the cost of IV therapy. The only problem however is the more tedious way of inserting the cannula since the skin site can have more glare from the shiny ointment once applied as reported by the residents and interns who participated in the study. However, if proven by further studies and by evidenced based medicine, the decreased cost of reinsertion and decreased pain for the patient can be beneficial.

REFERENCES

1. Lai. Safety of prolonging peripheral cannula and i.v. tubing use from 72 hours to 96 hours. Am J Infect Control 1998 Feb; 26 (1): 66-70
2. Shimandle, Johnson, Baker, Stotland, Karrison, Arnow. Safety of peripheral intravenous catheters in children. Infect Control Hosp Epidemiol 1999 Nov; 20(11): 736-40
3. Stephen, Loewenthal, Wong, Benn. Complications of intravenous therapy. Med J Aust 1976 Oct 9; 2(15): 557-9
4. Tager, Ginsberg, Ellis, Walsh, Dupont, Simchen, Faich. An epidemiologic study of the risks associated with peripheral intravenous catheters. Am J Epidemiol 1983 Dec;118 (6): 839-51
5. Palefski, Stoddard. The infusion nurse and patient complication rates of peripheral-short catheters. A prospective evaluation. J Intraven Nurs 2001 Mar-Apr; 24(2): 113-23
6. Oishi. The necessity of routinely replacing peripheral intravenous catheters in hospitalized children. A review of literature. J Intraven Nurs 2001 May-Jun; 24 (3); 174-9
7. Homer, Holmes. Risks associated with 72- and 96-hour peripheral intravenous catheter dwell times. J Intraven Nurs 1998 Sep-Oct; 21(5): 301-5
8. Tobin. The Teflon intravenous catheter: incidence of phlebitis and duration of catheter life in the neonatal patient. J Obstet Gynecol Neonatal Nurs 1988 Jan-Feb; 17 (1): 35-42
9. Garland, Dunne, Havens, Hintermeyer, Bozzette, Wincek, Bromberger, Seavers. Peripheral intravenous catheter complications in critically ill children: A prospective study Pediatrics 1992 Jun; 89 (6 Pt 2): 1145-50
10. McKee, Shell, Warren, Campbell. Complications of intravenous therapy: a randomized prospective study – Vialon vs. Teflon. J Intraven Nurs 1989 Sep-Oct; 12(5): 288-95
11. Karadag, Gorgulu. Effect of two different short peripheral materials on phlebitis development.J Intraven Nurs. 1998 Sep-Oct; 1 (5):301-5
12. Maki, Ringer. Risk factors for infusion-related phlebitis with small peripheral venous catheters. Ann Inter Med 1991 May 15; 114 (10): 845-54
13. Catney, Hillis, Wakefield, Simpson, Domino, Keller, Connely, White, Price, Wagner. Relationship between peripheral intravenous catheter Dwell time and development of phlebitis and infiltration. J Infus Nurs 2001 Sep-Oct; 24(5): 332-41
14. Pettit, Kraus. The use of gauze versus transparent dressings for peripheral intravenous catheter sites. Nurs Clin North Am 1995 Sep; 30 (3): 495-506
15. Righter, Bischop, Hill. Infection and peripheral venous catheterization. Diagn Microbiol Infect Dis 1983 Jun; 1 (2); 89-93.

Table 2. Subjects in theMupirocin group who developed phlebitis and the type of infusate given

Mupirocin

Subjects with phlebitis	Type of infusate		
	IV fluids	Antibiotic	Others IV meds
1	D5 0.3 Nacl		Furosemide
2		Penicillin G	
		Choramphenicol	
3	pNSS	Cefepime	
		Metronidazole	plt conc
4	D5 0.3 Nacl		plt conc

C. Number of times the IV cannula were used

There could be several attempts in IV insertion in a subject and a cannula could be used several times by the intern or the residents before a successful cannulation. Majority of IV insertion fortunately was successful on first attempt. Seven out of 51 of those who developed phlebitis had the IV cannula used only once in an attempt. There were 2 subjects whose cannula was used 4 times but did not developed phlebitis.

Table 4. No of times the cannulla has been used and the incidence of phlebitis

No. of Times the IV Cathwas used	Mupirocin		Control	
	# of Subjects	+ Phlebitis	# of Subjects	+ Phlebitis
1	30	5	21	2
2	3	1	10	2
3	1	1	2	0
4	2	1	0	0

D. Type of Personnel Performing the cannulation.

In PGH pediatric wards and emergency room, the interns were the first in line who should perform the IV insertion, thus 70% (36/53) of the IV insertion were performed by the interns while the rest were done by the residents. Seven out of the 36 insertions done by the interns developed phlebitis while 4 out of the 18 insertions done by the residents had phlebitis.

Table 5. The type of personnel performing the IV cannulation and the incidence of phlebitis

Type of Personnel	Control		Mupirocin	
	# of Subjects	+ Phlebitis	# of Subjects	+ Phlebitis
Interns	24	4	20	3
Residents	13	4	13	1

DISCUSSION

Phlebitis is the most common complication of IV therapy and several factors has been implicated in its pathogenesis. Chemical factors such as irritant drugs and physical factors such as duration of cannulation are just few of the identified risk factors for the development of phlebitis.

Among the 69 subjects both in the control and mupirocin group evaluated in this study, 12 developed phlebitis thereby giving an incidence rate of 17%. This is within range of the incidence of phlebitis reported in other studies which is from a low of 2.3% to a high 31%.[1,2,3,4] For those in the control group, 22% (8/36) developed phlebitis, a rate that is higher than in the case group with 12% (4/33). With using topical topical mupirocin the absolute risk reduction is 10% and the relative risk reduction of 46%. The results therefore suggests that applying topical mupirocin (Bactroban) in the IV insertion site may the decrease the risk of phlebitis. However, using the statistical analysis Fisher's exact test this finding is not statistically significant with a 2-tail p value of 0.34781

The rationale for the use of topical antimicrobial in the preparation of the skin for IV insertion can decrease the bacterial load of the skin thus decreasing the colonization in the point of entry. Topical antimicrobial is often employed in the care of central venous catheter but its use in percutaneous IV cannulation is not by standards observed. Some studies even discourage the use of antimicrobial ointment because it can result in higher incidence of phlebitis.

The length of time that the IV cannula is in place is traditionally believed to be directly correlated with the incidence of phlebitis. Two subjects however whose dwell time exceeds 144 hours did not developed phlebitis although 2 subjects with dwell time of 121-144 hours did. Five subjects in the control group with dwell time less than 48 hours had phlebitis. The per day risk of phlebitis is not evident in this study and this supports the no longer acceptable practice of replacing IV cannula every three days.

In this study, the IV insertion performed by interns showed 16% (7/44) rate of phlebitis as compared with residents who had 19% (5/26). In PGH, it is usually the interns who were first in line to do the IV insertion and the procedure would be referred to the residents in cases of difficult insertion. The higher rate of phlebitis among those done by residents can be probably explained by their more difficult tasks of IV insertion especially among chronic patients.

The catheters were subsequently handled according to the normal practice of the attending medical and nursing staff. Each patient was seen daily by the investigator and the patient was questioned about pain in the insertion site, or/and the IV site was inspected and palpated. The presence of phlebitis was defined as the presence of a palpable cord or the presence of at least 2 of the following physical changes along the course of the vein: warmth, erythema, tenderness and induration.

RESULTS

Of the 92 patients enrolled in the study, only 36 in the control group and 33 in the case group were included in the evaluation. Twelve patients in the control group out of 48 (25%) and 11 out of the 44 (25%) patients in the case group were excluded because their IV cannula were removed in less than 24 hours or the patients were discharged before the investigator was able to assess the IV site. Subject characteristics for both groups were similar with respect to sex although there in terms of age, there were more subjects in the 1 to 12 months age group among the control. For both control and case group, the locations of the IV insertions had almost similar distribution and most were done in the hand. Final result had shown that 8 out of the 36 (22%) subjects in the control group developed phlebitis as compared to the case group in whom 4 out of the 33 (12%) subjects had phlebitis.

Subject Characteristics:

Control		*Mupirocin*	
I. **Sex:**		I. **Sex:**	
Male	19	Male	20
Female	12	Female	13
II. **Age Group**		II. **Age Group**	
0-<1mo	3	0-<1mo	3
1-12mos	19	1-12mos	11
1-5yrs	6	1-5yrs	11
6-12yrs	7	6-12yrs	6
13-18yrs	1	13-18yrs	2
III. **IV Cannulation Site**		III. **IV Cannulation Site**	
Hand:		Hand:	
Right	15	Right	13
Left	8	Left	9
Forearm:		Forearm:	
Right	0	Right	0
Left	3	Left	4
Foot:		Foot:	
Right	5	Right	4
Left	4	Left	2
Leg:		Leg:	
Right	0	Right	0
Left	1	Left	0
Scalp:	0	Scalp:	1

A. Dwell time

The average dwell time for subjects in the control group is 62.9 hours (SD 30.3 hours) as compared to the case group with average dwell time of 62.8 hours (SD 30.4). If subjects whom IV cannula were electively removed or those whom cannulation where removed because they were no longer need for were excluded, the average dwell time became 62.7 hours (SD 29.9) for the control and 65 hours (SD 27.6) for the case group. Of the total of 12 patients who had phlebitis, 5 had their cannula in place for 24-48 hours, 3 of them for 49-72 hours, 2 for 73-96 hours while 2 had their cannula in place for 145-168 hours.

Dwell Time	Control		Mupirocin	
	# of Subjects	+ Phlebitis	# of Subjects	+ Phlebitis
24-48 hrs	16	5	14	0
49-72 hrs	10	2	10	1
73-96 hrs	4	1	5	1
97-120 hrs	4	0	1	0
121-144 hrs	1	0	2	2
145-168 hrs	1	0	1	0

B. Type of Infusate

Of the 12 patients in the control group who developed phlebitis, 8 were given IV fluids while 4 had heparin lock. Eight were given IV antibiotics while 3 were given blood products.

Table 2. Subjects in the control group who developed phlebitis and the type of infusate given

Control Group

Subjects with phlebitis	**Type of infusate**		
	IV fluids	Antibiotic	Others IV meds
1	D5 0.3 NaCl		Mannitol, Dexamethasone
2	D5 IMB	Ampicillin, Metronidazole	Famotidine
3	D5 IMB	Penicillin G, Amikacin	Vitamin K, Paracetamol
4		Meropenem	
5		Piperacillin-Tazobactam	Midazolam
6	pNSS		pRBC
7	D5IMB + K2 + Ca200	Meropenem	Famotidine
8	D5IMB	Ampicillin, Amikacin	Vitamin K

in an attempt at successful cannulation. A transparent polyurethane cannula (Insyte) is the most commonly type of used which compared to butterfly steel cannula is said to decrease the risk of phlebitis.[10, 11, 12]

A significant factor in the development of phlebitis is the infusate or the type and frequency of medication or fluid infused and pushed. Drug irritation is the most reliable predictor of phlebitis.[13] Total parenteral nutrition, blood products, potassium and sodium bicarbonate drips are just some of the infusate commonly implicated in phlebitis.

There are commercially available IV cannula dressings available in the market such as transparent dressing and sterile gauze but these are more expensive and thus has not been popularly used. The use of gauze versus transparent dressing shows no relationship with IV complications such as bacterial colonization and phlebitis although a study has shown less evidence of phlebitis with adhesive bandage compared with gauze.[14,3] Bacterial colonization or the presence of positive culture in the cannula tip is widely believed to be not correlated with the development of phlebitis.[15] There has been no reported study comparing these commercially available dressing with adhesive tape (Leukoplast) which is generally what is being used in PGH.

The most practical way of preventing phlebitis is the employment of aseptic technique in the performance of the peripheral IV cannulation procedure. The usual practice in this institution is to topically clean the area in the skin with alcohol and the secure the site with leukoplast. Application of a topical antibiotic prophylactically in the insertion site such as mupirocin ointment is not usually done except although occasionally, povidone iodine, a topical antiseptic is used. Some studies, however has shown that the use of antimicrobial ointment has resulted in higher proportion of phlebitis.[16]

Mupirocin, a topical antibiotic available in ointment form has been used in the treatment of secondarily infected wounds. It is likewise often used in the care of indwelling central lines to prophylactically prevent phlebitis or even treat secondarily infected central line site. It is effective against gram positive and gram negative organisms including methicillin resistant *Staphylococcus aureus*. As to date, there is no local study investigating the efficacy of the application of mupirocin in the prevention of the development of superficial phlebitis in peripheral cannulation site.

OBJECTIVES

The primary objective is to assess whether single topical application of mupirocin ointment in the peripheral IV cannulation site administered prior to IV cannulation compared to applying alcohol alone decreases the incidence of phlebitis.

Secondary objectives include:

1. to determine and assess the factors that predisposes to the development of superficial phlebitis namely:

a. the length of time the IV cannula is in place
b. the type of IV medications infused
c. the number of attempts before the cannula has been inserted
d. the type of personnel (i.e. intern, resident) who performed the cannulation

Type of Study

A randomized controlled trial in which mupirocin ointment topically applied prior to IV cannulation is compared with using alcohol alone.

Participants

Patients in the pediatric wards and emergency room requiring indwelling peripheral IV cannulation for more than 24 hours.

Exclusion Criteria

Patients whom IV cannula was removed within 24 hours from insertion.

Outcome Measures

The presence of signs of phlebitis in the area where IV cannulation has been placed as assessed by the investigator.

METHODOLOGY

All patients in the emergency room and wards for intravenous catheter insertion that was referred for inclusion in the study was randomly assigned to case group or control group. For every patient enrolled in the study a card was drawn from a set of cards randomly marked with “B” and unmarked cards. Those assigned with unmarked cards was put in the control group while those with marked “B” was placed in the case group

The choice of IV site for each patient was at the discretion of the physician and or intern as is the choice of the IV catheter to be used. The insertion technique was done percutaneously without prior skin incision. The skin was prepared with alcohol. All patients in the case group will have topical mupirocin applied to the area covering at least 0.25 cm prior to IV insertion. The insertion site would then covered with an adhesive tape.

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THE EFFECT OF TOPICAL APPLICATION OF MUPIROCIN IN INTRAVENOUS CATHETER SITE IN THE INCIDENCE OF SUPERFICIAL PHLEBITIS

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ABSTRACT

Background: Superficial phlebitis is a common complication of venoclysis although its incidence especially in pediatric hospital setting is not often known and evaluated. A standard aseptic technique in IV line insertion is observed to decrease its incidence but the use of topical antibiotic is rarely used.

Study objectives: Our objective was to determine if topical application of antibiotic mupirocin will affect the incidence of superficial phlebitis as compared to using alcohol alone in the preparation of the IV insertion site.

Setting: Pediatric department wards and emergency room of the University of the Philippines-Philippine General Hospital.

Methodology: In a randomized control study, 69 pediatric patients for intravenous catheter insertion were evaluated. Thirty-six patients were assigned in the control group whose IV insertion site were prepared with alcohol alone while 33 patients in the case group received topical mupirocin after application of alcohol in the IV insertion site. The IV insertion site were than evaluated daily by the investigator for the development of superficial phlebitis until the IV cannula were removed.

Results: Eight out of the 36 patients (22%) in the control group while 4 out of the 33 patients (12%) in the case group developed phlebitis.

Conclusion: The use of topical mupirocin in the IV insertion site prior to cannulation can decrease the incidence of superficial phlebitis.

Background

Phlebitis in insertion site is not an uncommon complication of peripheral intravenous catheterization with cases reported to range from a low 2.3% to as high as 31%.[1,2,3,4] It can manifest as an inflammation in the insertion site to cellulitis and suppuration in the contiguous areas to a more severe catheter related sepsis.

In UP-PGH pediatric wards and emergency room, a proper and successful IV catheter insertion is one of the most basic skill that interns and residents should learn. This can be made difficult by the fact that peripheral veins of pediatric patients are small and often difficult to locate visually and by palpation. Formal IV therapy training for hospital personnel has been shown to decrease leakage, phlebitis and infiltration complications of IV cannulation.[5] In PGH, however, most medical interns learn the technique by practice while serving their rotation in the pediatrics department.

A proper and effective way of doing IV catheterization entails an aseptic technique that every health personnel performing the procedure should observe. However, the incidence of phlebitis may still occur in the insertion site requiring the removal of the IV cannula and reinsertion of new cannula in another site.

Several factors may predispose to the development of superficial phlebitis in IV cannulation site foremost of which is the length of time the cannula is in place or the dwell time. The Center for Disease Control guidelines recommends replacement of IV catheter every 48 to 72 hours for adults but no such recommendation for pediatric patients exists.[6] Studies however has shown that there is no significant differences between phlebitis rate of cannula with dwell time of 72 hour and 96 hour.[7,1] Thus, considering the difficulty of successful cannulation, the limited number of skin sites, and the cost of the devise, the cannula may be left in place for longer than 48 hours.[9] Among neonates, catheter life is on the average lasts for only 30 hours. Extravasation, erythema, accidental displacement, and worse, phlebitis may require the removal and reinsertion into another site of the cannula. Without these complications however, catheter can be safely maintained with adequate monitoring for up to 144 hours.[3]

It is advisable that IV cannula should be used only once per attempt but this is not always the case in PGH where the same cannula can be used several times

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Key Words: *intravenous cannulation, mupirocin, pediatrics, superficial phlebitis, topical antimicrobial*