Intrapartum and Neonatal Zidovudine Treatment in Reduction of Perinatal HIV-1 Transmission in Bangkok

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Abstract

Objective : To evaluate the efficacy of zidovudine (ZDV) administered during labor and to the infants in the first 6 weeks of life in reduction of perinatal HIV-1 transmission.

Design : Open label clinical trial.

Site : King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Material and Method : One hundred asymptomatic, antiretroviral naïve HIV-1 infected pregnant women who had either late or no prenatal care were recruited from the obstetric service of King Chulalongkorn Memorial Hospital, Bangkok, Thailand. They were given ZDV 300 mg orally every 3 hours during the intrapartum period until delivery. ZDV syrup 2 mg/kg orally every 6 hours were given to the infants immediately after birth for 6 weeks. Breast feeding was not allowed. Infant's blood for HIV-1 PCR test was obtained at age 1 day, and 1, 3 and 6 months. HIV-antibody test was determined at age 18 months. Infants with at least one positive HIV-1 PCR test performed at or after 1 month of age or positive HIV–antibody test at age 18 months were classified as HIV-1 infected infants.

Results : There were 100 healthy infants delivered without complication. Fourteen infants were excluded due to; 13 lost to follow-up and 1 drug intolerance. Of the remaining 86 infants who were followed-up, 27 infants (31.4%) did not receive intrapartum ZDV treatment and 9 infants were HIV-1 infected. The perinatal transmission rate was 10.5 per cent, (95% CI 3.9, 17.1).

Conclusion : The result of this study suggests that intrapartum oral ZDV treatment in asymptomatic HIV-1 infected mothers together with ZDV treatment in the neonates for 6 weeks can reduce the rate of perinatal HIV-1 transmission. This regimen may be an alternative treatment for prevention of HIV-1 infection in infants born to HIV-1 seropositive mothers who have had either late or no prenatal care.

Key ward : Perinatal Transmission, HIV, Intrapartum Treatment, Neonatal Treatment

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Perinatal transmission is the major route of acquired HIV-1 infection in children. The transmission rate in the absence of breast feeding reported in Thailand is approximately 19-25 per cent[1,2]. Significant reduction of mother-to-infant transmission rate has been demonstrated in the zidovudine (ZDV) prophylactic treatment regimen of ACTG 076 protocol[3] as well as many modified shorter courses of ZDV treatment[2,4,5]. These regimens of treatment are still too complex and non-affordable for some patients in developing countries. Although the Thai Red Cross zidovudine donation program offers the drug at no cost to HIV-1 infected pregnant women and their infants throughout Thailand[5], there are a number of pregnant women who have either late or no prenatal care will not get access to the program.

Recent evidence suggests that about 60 per cent of HIV infected infants are infected at or just before birth[6-8]. We have demonstrated previously that a short course ZDV maternal treatment initiated at 38 weeks' gestation plus intrapartum ZDV infusion without treatment in the neonate was not effective to prevent HIV-1 vertical transmission[9]. Therefore, it was speculated that ZDV prophylaxis begun at the time of HIV-1 exposure during labor and neonatal treatment immediately after birth might have potential efficacy in decreasing HIV infection in the infants. Wade et al[10] reported that when ZDV treatment was started during the intrapartum period or within the first 48 hours of life, perinatal HIV-1 transmission rates were 10.0 per cent (95% CI 3.3, 21.8) and 9.3 per cent (95% CI 4.1, 17.5) respectively. However, this study was limited by its observational nature and by the small number of infants in the validation samples. The confidence intervals were rather wide, so the exact degree of reduction in the transmission rate was not quite clear. So, the authors conducted a prospective study to determine whether intrapartum and neonatal zidovudine treatment could be effective in a larger number of pregnant women who have either late or no prenatal care in Bangkok, Thailand.

MATERIAL AND METHOD

Known HIV-1 seropositive, antiretroviral naïve pregnant women with either late or no prenatal care were recruited from the Obstetric service of King Chulalongkorn Memorial Hospital, Bangkok between February 1997 and March 2000. Women with late prenatal care were those who first came to the prenatal clinic at or more than 38 weeks of pregnancy. HIV-1 infected status was determined by rapid HIV antibody test in maternal serum using enzyme linked immunoassay (ELISA) method and confirmed by gel particle agglutination test (Serodia test) if the ELISA test was positive at the first visit to the prenatal care clinic or as soon as the mother was admitted to the labor room. After counseling and written informed consent was given, the women who were in labor and met the entry criteria, would receive zidovudine 300 mg orally every 3 hours until delivery. Zidovudine syrup 2 mg/kg orally every 6 hours was given to the infants for 6 weeks. The drug was begun immediately after the infant had been stabilized. Breast feeding was not allowed and infant formula was provided.

Entry criteria included : (i) HIV-1 seropositivity in pregnant women as documented (ii) no *prior* antiretroviral treatment and (iii) ability to bring the child for long term follow-up. Women and infants were assessed for possible drug toxic effects and adverse events according to the ACTG adverse events monitoring guide. At each visit the infant had a physical examination and was evaluated for adverse events or complications. The amount of ZDV syrup left in the bottle at the first visit (aged 1 month) was reviewed to determine the mother's compliance. The infants received appropriate medical care and vaccination until the age of 2 years. Serial blood samplings for detection of HIV-1 proviral DNA at age 1 day, 1, 3, 6 months and HIV-1 antibody at age 18 months were obtained. Nested polymerase chain reaction (PCR) for the detection of HIV-1 proviral DNA (env and poly genes) was performed as previously described[11]. Infants with at least one positive PCR test at age 1 month or more or with positive HIV-1 antibody test at 18 months were defined as HIV infected infants[12]. HIV-non-infected infants were those with negative results of these tests and also had no HIV related symptoms.

The SPSS version 8.0 package (SPSS Inc. Chicago, Illinois, U.S.A.) was used for data analysis. The perinatal transmission rate with exact binomial 95 per cent confidence interval (CI) was calculated.

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

RESULTS

One hundred pairs of mothers and infants were enrolled. All infants were healthy singletons, and live born without congenital anomalies. There was no neonatal death and no infant mortality during the follow-up period. Fourteen infants were excluded because; 13 of them were lost to follow-up, they didn't come back after they left the nursery and one infant was unable to tolerate oral zidovudine. This infant developed anemia and diarrhea with dehydration on the 7th day of life.

All of the HIV-1 infected mothers were asymptomatic and the majority of them were housewives, Fifty mothers were primiparous. Mean ± S.D. of maternal age was 25.6 ± 4.8 years (range 19-40 years). Complication of pregnancy included; 2 intravenous heroine addicts, 2 syphilis, 1 herpes genitalis infection and 3 cases of prolonged ruptured membranes (≥ 24 hours). Cesarean section was performed on 17 mothers. The indications were cephalopelvic disproportion, prolonged ruptured membranes, herpes genitalis infection, severe maternal hypertension, and previous cesarean section. Eighty three mothers had vaginal deliveries with 8 assisted modes (6 forceps extraction and one each of vacuum extraction and breech assistance). Intrapartum zidovudine was not given to 36 mothers. Of 64 mothers with intrapartum treatment, 26 of them (40.6%) received only 1 dose of the drug. Ninety seven infants were full term and 3 were premature (all had 36 weeks' gestation). Ratio of male to female was 49:51. Mean ± S.D. of birth weight was 3056 ± 408 grams (range 2300-4290 grams). Mean ± S.D. of time of the initiation of neonatal zidovudine treatment was 1.9 ± 2.6 hours (range 0.25 – 17 hours). Demographic characteristics of both mothers and infants are summarized in Tables 1 and 2.

Eighty six infants who remained on the study, had good drug compliance and were analyzed for the transmission rate. Twenty seven mothers of these infants did not receive intrapartum ZDV treatment. HIV infection was diagnosed in 9 infants. The overall perinatal transmission rate was 10.5 per cent (95% CI, 3.9, 17.1). Fifty two infants were followed until the age of 18 months when the HIV-1 antibody test was performed. The result the of HIV- antibody test corresponded with the HIV-PCR test. Eight infants with positive HIV-PCR test also had positive HIV antibody test, (Table 3). Among the HIV-1 infected infants, 6 were delivered spontaneously, 3 were delivered by cesarean section indicated by cephalo-pelvic disproportion. One HIV-1 infected infant was premature (2,300 grams), and another one had no intrapartum ZDV treatment. When zidovudine treatment was begun intrapartum, 8 of 59 infants were HIV infected, the transmission rate was 13.6 per cent (95% CI 4.7, 22.5). Only one of 27 infants whose mothers did not receive intrapartum treatment developed HIV-1 infection, the transmission rate was 3.7 per cent (95% CI 3.6, 11.0). HIV related symptoms of infected infants included generalized lymphadeno-

Table 1. Characteristics of mothers.

Characteristics	Number or Mean ± S.D. (Range)
Number of enrollments	100
Age (years)	25.6 ± 4.8 (19-40)
Gravida : 1	50
2	32
3-7	18
Type of delivery	
vaginal	83
cesarean section	17
Intrapartum ZDV treatment	
yes	64
no	36

Table 2. Characteristics of infants.

Characteristics	Number or Mean ± S.D. (Range)
Total number of infants	100
Number of drop outs	14
Number of eligible infants	86
M : F	49 : 51
B.W. (grams)	3056 ± 408 (2300-4290)
Age at initiation of neonatal ZDV treatment (hours)	1.9 ± 2.6 (0.25-17)

Table 3. Infants' outcome.

	Number	%
Eligible infants	86	
Number of infants with positive HIV-PCR	9	10.5
Number of infants who had HIV antibody test at 18 months	52	60.5
Number of infants with positive HIV antibody test	8	

pathy, failure to thrive, hepatosplenomegaly, oral and cutaneous moniliasis. Lymphadenopathy was the most common and earliest clinical finding which was noted by 3 months of age. Three HIV infected infants remained asymptomatic at 18 months. None of 77 infants with negative HIV-PCR test had HIV related symptoms and 44 of them also had negative HIV-1 antibody test.

DISCUSSION

The present findings suggest that infants born to HIV-1 infected mothers who have either late or no prenatal care may gain some protective effect from intrapartum and/or neonatal zidovudine treatment. The vertical transmission rate in the entire cohort was 10.5 per cent (95% CI 3.9, 17.1). It indicates that this prophylactic regimen can reduce the incidence of perinatal HIV-1 infection by approximately 50 per cent compared with the historical data reported in Thailand[1,2]. Although when zidovudine is begun intrapartum, the transmission rate is higher than that of neonatal treatment alone, (13.6% *vs* 3.7%). This could be an error which occurred by chance and the number of infants in each subgroup was limited. Intrapartum zidovudine treatment in this study was probably not quite efficient enough, because the drug was begun rather late after the onset of labor. Twenty six (40.6%) mothers received only one dose just prior to delivery.

Intrapartum events that increase fetal exposure to maternal blood include mode of delivery, duration of labor, presence of antepartum hemorrhage, maternal sexually transmitted diseases and chorioamnionitis have been correlated with HIV-1 transmission rate[13,14]. Obstetric practice must influence more on the outcome of the infants. Several studies have suggested that elective cesarean section may be associated with a decrease in perinatal transmission[15,16]. We could not demonstrate the protective effect of cesarean section against HIV-1 transmission in our cohort. Because cesarean section was performed after the onset of labor in all of our patients. Prolonged labor was noted in 4 infected infants. Three out of 14 infants (21.4%) delivered by cesarean section were HIV-1 infected, whereas, 6 out of 72 infants (8.3%) with vaginal delivery were infected.

In the present study, maternal virologic and immunologic assays were not determined, so the impact of these factors upon the risk for vertical transmission could not be evaluated. However, zidovudine therapy has been shown to be effective in reducing perinatal HIV-1 transmission regardless of maternal viral load[17,18].

Pregnancy without prenatal care is a common practice among women with low socio-economic status in Thailand[19]. Poverty and ignorance are the major factors which preclude them from seeking proper medical care. Most of our patients were poor. They migrated from different parts of the country to Bangkok looking for jobs. When the country faced an economic crisis recently, they had to move away. Unfortunately, we conducted the study during this certain time period. The lost to follow-up infants' addresses could not be located. Thus, for these reasons there was a high drop out rate (14%) in the present study. The authors believe that tremendous effort is required to help these poor infants. All HIV-1 seropositive pregnant women should be encouraged to have early prenatal care with proper counseling and adequate antiretroviral prophylactic treatment. The authors realize that the treatment regimen in this study can not replace a prophylactic regimen of all 3 parts of treatment including prenatal treatment, because at least 1/3 of the vertical HIV-1 transmission occurring *in utero* is not prevented.

Gauy et al[20] reported another alternative prophylaxis by using a single dose of nevirapine. It was found that a single dose of oral nevirapine administered at the onset of labor to HIV-1 infected women and to infants within 72 hours of life, significantly lowered the risk of HIV-1 perinatal transmission than that of a short course of zidovudine administered over a similar time period. This strategy may be more practical for prevention of HIV-1 perinatal transmission in infants born to mothers with either late or no prenatal care. However, the result of the present study is consistent with the observational data described by Wade et al (10) and it demonstrates that intrapartum and neonatal zidovudine treatment still provides some protective effect and can have some use in this group of patients.

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ลดการแพร่เชื้อเอ็ชไอวีจากมารดาสู่ทารกด้วยการให้ยาซิโดวูดีนแก่มารดาขณะรอคลอดร่วมกับการให้ทารกระยะหลังคลอด : ศึกษาที่กรุงเทพฯ

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ทำการศึกษาประสิทธิผลของการให้ยา zidovudine (ZDV) แก่มารดาที่ติดเชื้อเอ็ชไอวี ในระยะรอคลอดร่วมกับการให้ยาน้ำ ZDV แก่ทารกหลังคลอด เพื่อลดอุบัติการณ์การแพร่เชื้อเอ็ชไอวีจากมารดาสู่ทารก มารดาเหล่านี้มาฝากครรภ์ช้าเมื่อใกล้กำหนดคลอดหรือไม่เคยฝากครรภ์ที่โรงพยาบาลจุฬาลงกรณ์และไม่เคยได้รับการรักษาด้วยยาต้านไวรัสเอ็ชไอวีมาก่อน ขณะเจ็บครรภ์จนกระทั่งคลอดจะได้รับประทานยา ZDV 300 มิลลิกรัมทุก 3 ชั่วโมง ทารกจะได้รับประทานยาน้ำ ZDV ขนาด 2 มิลลิกรัม/กก. ทุก 6 ชั่วโมงทันทีหลังคลอดเป็นเวลานาน 6 สัปดาห์ ทารกทุกคนไม่ได้รับการเลี้ยงด้วยนมแม่ เจาะเลือดทารกตรวจ HIV-PCR เมื่ออายุ 1 วัน 1, 3, 6 เดือน และตรวจแอนติบอดีย์เอ็ชไอวีเมื่ออายุ 18 เดือน ทารกได้รับการวินิจฉัยว่าติดเชื้อเอ็ชไอวี ถ้ามีผลตรวจ HIV-1 PCR เป็นบวกอย่างน้อย 1 ครั้งจากเลือดที่เจาะเมื่ออายุ 1 เดือนหรือมากกว่า หรือผลแอนติบอดีย์เอ็ชไอวีเมื่ออายุ 18 เดือนเป็นบวก

ผลการศึกษาพบว่า มีจำนวนทารกเกิดจากมารดาเหล่านี้ 100 คน ไม่มีทารกคนใดเสียชีวิตหรือพิการ ทารก 14 คน ถูกคัดออกจากการศึกษา เนื่องจากทารก 13 คน ขาดการติดต่อตั้งแต่ออกจากโรงพยาบาลอีกคนหนึ่งแพ้ยา ZDV ทารก 9 คน ติดเชื้อเอ็ชไอวี-1 คิดเป็นอัตราการแพร่เชื้อจากมารดาสู่ทารกเท่ากับร้อยละ 10.5 (ช่วงความเชื่อมั่น 95% เท่ากับ 3.9,17.1) มารดา 27 คน (31.4%) ของทารกเหล่านี้ไม่ได้รับยา ZDV ขณะรอคลอด

การศึกษานี้แสดงให้เห็นว่าการให้ยา ZDV แก่มารดาขณะรอคลอดและให้ยา ZDV แก่ทารกเป็นเวลานาน 6 สัปดาห์ สามารถลดอัตราการแพร่เชื้อจากมารดาสู่ทารก อาจใช้วิธีนี้ป้องกันภาวะติดเชื้อเอ็ชไอวี ในทารกที่เกิดจากมารดาที่ติดเชื้อนี้แต่ฝากครรภ์ช้า เมื่อใกล้กำหนดคลอด หรือไม่เคยฝากครรภ์มาก่อนได้

คำสำคัญ : การแพร่เชื้อจากมารดาสู่ทารก, เอ็ชไอวี, การให้ยาแก่มารดาขณะรอคลอด, การให้ยาแก่ทารก

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