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Cord Blood Diazepam : Clinical Effects in Neonates of Eclamptic Mothers

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Abstract. Diazepam used in the treatment of eclampsia crosses the placental barrier readily, and may cause various clinical effects in the neonates. Twenty-five (25) live born babies of eclamptic mothers receiving diazepam were studied and cord blood diazepam concentration was estimated. Effect of low dose of diazepam is minimal apart from lowering of rectal temperature and the effects lasted for a period of 12 hours. But high dose (> 30mg) of diazepam and prolonged duration of diazepam therapy in mothers causes significant depression of the newborn and the effects lasted for a period of 36-48 hours. As the clinical condition of the newborn is not related to the diazepam concentration in cord blood, the cord blood estimation is not helpful in the assessment of clinical effects of the drug in newborn. The tissue storage of the drug in newborn appears to be responsible for the clinical effects. **(Indian J Pediatr 1993; 60: 257-263)**

Key words : *Eclampsia; Diazepam therapy; Cord blood diazepam; Neonatal effects.*

One of the important component of therapy in eclampsia is the administration of anticonvulsant drugs. Among these, diazepam causes prompt control of convulsions and is proved to be safe for mother as well as foetus.[1] Diazepam crosses the placental barrier readily when administered to mother, and may cause various neonatal problems such as low apgar score, apnoeic spells, respiratory depression, lethargy, hypotonia, hyporeflexia, reluctance to feed hypothermia, hyperbilirubinaemia, tremor and hyper-reactivity.[2,3,4] These effects are related to the drug dose and duration of therapy.[3,4] Therefore, the objective of the present study is, (i) to assess the clinical condition of the newborn of eclamptic mothers treated with diazepam, (ii) to assess the relationship between the total dose and duration of diazepam therapy before delivery and its effects on the newborn, and (iii) to evaluate any relationship existing between the cord blood diazepam concentration and the clinical condition of the newborn.

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MATERIAL AND METHODS

Eclamptic mothers receiving parenteral diazepam therapy were selected. Twenty-five (25) live born babies of these eclamptic mothers having gestational age from 32 weeks upto term, having birth weight of 1.5 kg and above, and without any congenital anomaly were selected. Newborns were grouped as *Group I* : Mothers who received a low dose of diazepam (≤30 mg) within 15

hours before delivery. *Group II* : Mothers who received a high dose of diazepam (>30 mg) before delivery. *Group IIA* : Duration of diazepam therapy within 15 hours before delivery. *Group IIB* : Duration of diazepam therapy more than 15 hours before delivery.

Twenty five (25) normal newborn babies, having same gestation as the study group were selected for control study. A detail history of mother including antenatal period and drugs administered to her was taken. Total dose of diazepam (continuous I.V. infusion and I.V. injections) and duration of diazepam therapy was noted. Thorough clinical examination of the neonates including apgar score at 1 and 5 minutes, and rectal temperature at 30 minutes was done.

Clinical follow up during the first week of life was done. Symptoms attributable to diazepam, e.g. rectal temperature, respiratory effort, muscle tone and sucking reflex were specially recorded 4 hourly upto 24 hours, then 12 hourly from 24 to 72 hours after birth, then daily upto 7 days of life. At the time of delivery, 2 ml. umbilical cord blood was collected in heparinised vials, packed in dry ice and sent to Bose Institute, Calcutta, for analysis of diazepam content. Determination of diazepam in blood was done by the method described by De Silva et al.[5,6] Statistical analysis was done using student's 't' test (unpaired).

RESULTS

Among all the cases, 11 cases (44%) were preterm, 13 cases (52%) were LBW. Mean apgar score at 1 minute was 5.6 ± 1.68 and 8.2 ± 1.63 in the study and control group respectively ($p < 0.001$), and

TABLE 1. Clinical Details, Maternal Dose and Effects of Diazepam on Newborns in Group I : Low Dose (≤30mg) Short Duration (< 15hrs) of Diazepam Therapy (n=8)

Case no.	Total dose of diazepam (mg)	Duration of therapy (hrs)	Symptoms attributable to diazepam	Cord blood diazepam level μgm/ml
1.	10	½	Shallow, regular respiration, cry-absent; mod. hypotonia; poor reflexes	0.498
2.	10	1	-	0.371
3.	10	3	-	0.223
4.	20	2	-	0.317
5.	20	2½	Mod. hypotonia; poor reflexes	0.195
6.	25	3	Shallow, regular respiration; mod. hypotonia; poor reflexes	0.252
7.	30	1½	Mod. hypotonia	0.301
8.	30	12	Mod. hypotonia poor reflexes	0.212

5 minutes it was 7.7 ± 1.24 and 9.3 ± 0.99 in the respective group ($p < 0.001$). The mean rectal temperature was 34.8°C and 36.1°C in the study and control group respectively ($p < 0.001$). Among 20 cases having cord blood diazepam concentration less than 1,000 ng/ml, 19 cases (95%) had low rectal temperature (<35.6°C) including 11 (55%) hypothermic (< 35°C) cases. Among 5 cases having cord blood diazepam concentration more than 1,000 ng/ml, 4 cases (80%) had rectal temperature less than 35.6°C of which 2 cases were hypothermic. The Pearson coefficient (r value) between rectal temperature and cord blod diazepam concentration was 0.283 and the 't' value was 1.475 which is not significant ($p > 0.05$).

Among the major clinical features

TABLE 2. Clinical Details, Maternal Dose and Effects of Diazepam on Newborns in Group IIA: High Dose (> 30 mg), Short Duration (< 15 hrs) of Diazepam Therapy. (n =9)

Case no.	Total dose of diazepam (mg)	Duration of therapy (hr)	Symptoms attributable to diazepam	Cord blood diazepam level (µgm/ml)
1.	30*	1	Feeble cry: Mod. hypotonia; areflexia.	1.748
2.	35	1½	Rapid, irregular respiration; feeble cry; mod. hypotonia; poor reflexes.	0.401
3.	40	4	Irregular, shallow respiration; feeble cry; mod. hypotonia; poor reflexes	0.572
4.	40	5	Mod. hypotonia	0.432
5.	50	1½	Intubated; slow, shallow respiration; feeble cry; flaccid; areflexia.	0.344
6.	60	12	Intubated; shallow respiration; cry-absent; flaccid; areflexia.	0.645
7.	60	15	Feeble cry; mod. hypotonia poor reflexes	0.406
8.	80	12	Intubated; shallow respiration; cry-absent; flaccid; areflexia.	0.744
9.	80	14	Intubated; shallow, irregular respiration; cry-absent; mod. hypotonia; areflexia.	0.868

* (+ 5 mg tab b.i.d. × 6 days)

attributable to diazepam therapy, hypotonia (88%), abnormal respiration(52%) and feeble neonatal reflexes (76%) were observed in the study group (n = 25). Among the control group, these werefound in 24%, 8%, and 8% respectively.

Among the babies receiving low dose of diazepam (≤30 mg)for a short duration (n =8) [Table 1], none had low apgar score (< 5 at 1 min.). Low rectal temperture (35°C and below) was observed in all the cases among which 62.5% cases were hypothermic (< 35°C).

Among the babies receiving high dose of diazepam (> 30 mg) for a short duration(n=9) (Table 2), all babies failed to suck and required tube feeding or intravenous drip.

Among the babies receiving high dose of diazepam (> 30 mg) for a prolonged period (n = 8) [Table 3], 3 cases had temporary cessation of diazepam therapy for a few hours, and cord blood diazepam concentration was lower in them than other cases, but clinical symptoms did not vary.

TABLE 3. Clinical Details, Maternal Dose and Effects of Diazepam on Newborns in Group IIB; High Dose (> 30 mg), Prolonged Duration (> 15 hrs) of Diazepam Therapy (n =8)

Case no.	Total dose of diazepam (mg)	Duration of therapy (hr)	Symptoms attributable to diazepam	Cord blood diazepam level (μgm/ml)
1.	10*	32	Feeble cry; mod. hypotonia poor reflexes	1.443
#2.	70	75	Mod. hypotonia, poor reflexes	0.286
3.	90	35	Intubated; tachypnoea flaccid; areflexia	1.934
#4.	115	17	Tachypnoea; feeble cry; mod. hypotonia; poor reflexes	0.293
5.	120	16	Intubated; irregular hurried respiration; cry-absent; flaccid; areflexia	1.041
6.	140	25	Intubated; irregular shallow respiration; feeble cry;mod. hypotonia; poor reflexes	1.402
#7.	200	98	Intubated; irregular respiration; cry-absent; flaccid; areflexia	0.331
8.	240	68	Shallow, irregular respiration; feeble cry; mod. hypotonia; poor reflexes	0.647

Diazepam therapy was stopped temporarily for few hours in these cases.
* (+ 5 mg tab t.i.d. × 22 days)

TABLE 4. Relationship Between the Cord Blood Level of Diazepam and the Rectal Temperature (at 30 minutes) of Newborn

Cord blood level of diazepam (ng/ml)	Rectal temperature of the newborn (°C) (n = 25)				
	<34.4	34.4-34.9	35-35.5	35.6-36.1	36.2-36.7
≤200	-	-	1 (4)	-	-
201 - 400	5 (20)	2 (8)	3 (12)	1 (4)	-
401 - 600	2 (8)	2 (8)	1 (4)	-	-
601 - 800	-	-	3 (12)	-	-
801 - 1000	-	-	-	-	-
1001 - 1200	-	-	1 (4)	-	-
1201 - 1400	-	-	-	-	-
1401 - 1600	-	1 (4)	1 (4)	-	-
1601 - 1800	-	-	-	-	1 (4)
1801 - 2000	-	1 (4)	-	-	-

Figures in parentheses indicate percentage

Among the cases of low dose group (n = 8) (≤ 30 mg), 5 cases (62.5%) had hypotonia after birth, 3 cases (37.5%) regained normal tone within 12 hours. But in high dose (> 30 mg) group (n =17), all had hypotonia at birth which persisted for a prolonged period of 12-48 hours in 16 cases (94.1%). In the low dose group, initiation of oral feeding (62.5%), regainment of normal rectal temperature (100%) and normal respiration (100%) were observed within 12 hours after birth, but in high dose group these improvements were found after 36-48 hours, 12 hours and 36 hours respectively in the majority (> 90%).

Among 17 cases receiving high dose of diazepam therapy, 7 cases (41.1%) died, whereas, among 8 cases of low dose group (≤ 30 mg), 1 case (12.5%) died.

DISCUSSION

The mean apgar score in the study group was significantly low as compared to the control group. The low apgar score due to diazepam therapy was reported by many workers.[3,4,7,8,9] According to this, low apgar score of babies was related to hypotonic effect of diazepam, and was not indicative of central nervous system depression.[7]

Various workers have enunciated that diazepam therapy causes disturbed temperature regulation of neonates, and has got a tendency to produce lowering of temperature after its administration to the mother before labour.[9,10,11]

In this study, diazepam therapy in eclamptic mother causes significant decrement of rectal temperature. The probable mechanism of this low rectal tem-

perature due to diazepam was supposed to be due to either hypoxia or direct effect of the drug on the central temperature regulation centre or due to depression of muscle activity.[9] However, there was no correlation between the degree of hypothermia and cord blood diazepam concentration in this study. Owen et al[9] observed that plasma level of diazepam do not correlate with the rectal temperature of the newborn, whereas McAllister[11] observed a highly significant relationship existing between the rectal temperature of the newborn and the cord blood diazepam concentration.

Clinical effects of diazepam therapy was related to the dose and duration of therapy rather than the cord blood level.[3,11,12,13] Low dose (≤ 30 mg) of diazepam therapy in mothers within 15 hours before delivery had little or no effect on the newborn. High dose of diazepam (<30 mg) produces significant clinical effects, e.g. low apgar score, failing to start breathing, apnoeic spells, shallow inadequate breathing, hypotonia, subnormal temperature, poor sucking, similar to observations by others.[3,8] In high dose group, temporary cessation of diazepam therapy causes lowering of cord blood diazepam concentration without any significant change in clinical effects. Prolonged administration of diazepam in therapeutic doses in the mother produces similar clinical effects, and it is due to the fact that diazepam accumulates in the tissues of the foetus and is metabolized and excreted slowly in the newborn. Others were of opinion that presumably during prolonged administration, the foetal fat stores became saturated and after delivery the infants were unable to metabolize the existing drug in the system.[4,14]

Clinical effect due to diazepam in the low dose (≤ 30 mg) group persisted for 12 hours, whereas it was 36-48 hours in the high dose (> 30 mg) group.

Apart from the effects of the drug, various other factors such as proper obstetric management, resuscitation, biochemical management, maintenance of body temperature and infection, are related to the early neonatal mortality. Therefore, it is difficult to assess the actual effect of the drug on the early neonatal mortality.

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