PHENOTHIAZINE DERIVATIVES IN THE TREATMENT OF ECLAMPSIA—A FINAL ASSESSMENT

by

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Eclampsia still continues to be a major obstetrical problem in Madras. While during a five year period, 1929-1933, its incidence in the Women and Children's Hospital was 2.1%, during the latest five year period 1953-1957 it was still 1.6%. With the annual number of confinements exceeding 11,000 the magnitude of the problem becomes obvious.

It is not the aim of this paper to go into the history and details of the curative treatment of eclampsia. Suffice it to say that in modern obstetrics the treatment of eclampsia is essentially conservative. The principles in the management are to control convulsions by administration of sedatives, to reduce the blood pressure by hypotensive drugs, to help diuresis and by careful, intelligent and efficient nursing prevent injury during fits and other complications. The pregnancy is not interfered with except when in spite of continued conservative regime, the fits cannot be controlled. Under such circumstances labour is induced by artificial rupture of membranes. Caesarean section is forbidden except in the presence of cephalo-pelvic disproportion. Vaginal delivery is helped by outlet forceps to cut short the second stage.

From the early years morphia has been the one drug which has been used very largely in eclampsia. This, in conjunction with chloral, formed the sheet anchor of the Stroganoff regime. Later, various other sedatives were tried, either alone or in combination with morphia: paraldehyde, magnesium sulphate, barbiturates, bromethol, sodium thiopentone.

Following the changing trends we have treated a large number of eclamptics using different sedatives. Apart from morphia and chloral and bromides, we have used paraldehyde intramuscularly 7 ml. as the initial dose repeated every 4-6 hours in doses of 5-6 ml.; magnesium sulphate 25% solution 10 ml. intramuscularly alternately with $\frac{1}{4}$ gr. morphia every four hours and various other combinations. The details and results of treatment have been put forth in previous communications. The re-

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TABLE I

Sedative used	No. of cases treated	Incidence of recurrence of fits	Maternal mortality rate
Morphia, chloral and bromides ..	434	46%	18.6%
Paraldehyde intramuscular and morphia	204	41.6%	19.5%
Magnesium sulphate and morphia	105	36%	11.6%

sults of the use of some of these sedatives are briefly presented in Table I.

From 1938-1950 we treated 1151 cases of eclampsia using various combinations of sedatives. The results were disappointing in that the maternal mortality still continued to be high, average 15.1%, the range being 20% to 8.6%. Table II gives the annual maternal mortality rate from 1938-1950.

TABLE II

Year	No. of cases	No. of deaths	Mortality rate per cent
1938	86	16	18.5
1939	83	12	14.5
1940	55	11	20.0
1941	70	6	8.4
1942	21	3	12.8
1943	61	8	13.2
1944	66	7	10..6
1945	85	11	12.8
1946	108	20	18.5
1947	107	21	19.6
1948	104	19	18.2
1949	166	28	16.9
1950	139	12	8.6
Total	1,151	174	15.1

From October 1951, I started to treat all cases of eclampsia with sodium thiopentone on the lines suggested by Professor O'Donel Browne. The detailed observations and results of 75 cases treated by sodium thiopentone were published in 1953. I content myself by quoting a comment I then made which sums up my opinion on the sodium thiopentone therapy: "While pentothal (sodium thiopentone) may perhaps be the best drug in the control of convulsions it has not helped me in any way to reduce the maternal mortality. . . . From my experiences I am constrained to admit that the results obtained have not been commensurate with the stress and strain gone through". In a series of 75 cases so treated even though the recurrence rate of fits was reduced to 9.5%, the maternal mortality remained at 16.5% and I learnt that, to reduce the maternal mortality in eclampsia, control of convulsions alone was not sufficient.

A re-assessment of 174 maternal deaths from eclampsia (1938-1950) at this stage showed that ante-partum eclampsia has the maximum mortality, 17% as against 6.5% and 9.3% for intrapartum and post-partum eclampsia.

TABLE III

Type of eclampsia	No. of cases	No. of deaths	Percentage of mortality
Antepartum	826	145	17.5
Intrapartum	61	4	6.5
Post-partum	264	25	9.3

It also showed that in uncontrolled eclampsia the larger the time interval

between the onset of convulsions and delivery the greater the mortality.

TABLE IV

Time from first convulsion to delivery	Average mortality rate per cent
0 - 2 hours	7
2 - 4 „	12.8
4 - 8 „	18.6
8 -12 „	22
12-18 „	25
18-24 „	32
Over 24 „	42
Died undelivered	4.3

Forty of the ante-partum eclamptics died undelivered. These facts combined with the improvement which follows delivery in eclampsia which all of us have witnessed led me to consider the question of resorting to caesarean section in ante-partum eclamptics where conservative treatment failed to control convulsions in a reasonable time, 8 to 10 hours, that is in the severe type where the fits cannot be controlled and vaginal examination revealed a closed long cervix and an unengaged head indicating unfavourable response to induction by artificial rupture of membranes. Lower segment caesarean section under local anaesthesia was to be performed. In those exhibiting signs of favourable response only artificial rupture of membranes was to be done. In a series of 104 cases treated on these lines there were only five deaths, 4.8%. Twenty-five caesarean sections were done in this series with only one death, a death not attributable to the section. I was convinced that in properly selected cases under modern conditions caesarean section did not enhance the inherent mortality in eclampsia. On the other hand, it did help to reduce the maternal mortality. Where once caesarean section was denied I believe we could now offer it to these antepartum eclamptics who do not respond to conservative therapy. The place of caesarean section in eclampsia was presented in a publication in 1955.

At this stage the phenothiazine derivatives were made available. The pharmacological properties of the two drugs, Chlorpromazine (Largactil) and Diethazine (Diparkol), are only now well known. Amongst its important actions are its:

(a) ability to lower the body temperature—hypothermia,
(b) potentiating action of other drugs,
(c) hypotensive action,
(d) narcosis, and
(e) anti-shock property.

My experiences with the use of this drug have already been published in a number of communications. This is the final report on a large series of cases. The standard regime now employed for eclamptics is as follows:

On admission, 25 mgm. of Largactil and 100 mgm. of Pethidine in 20 ml. of 5% glucose are given intravenously. 50 mgm. of Largactil and 50 mgm. of Diparkol (Diethazine) are given intramuscularly. An intravenous drip of 20% dextrose solution containing 200 mgm. of Pethidine is then set up and this is run in slowly at twenty to thirty drops a minute, the rate depending upon the response to treatment. If the patient is quiet the rate of the drip is reduced, if she

is restless it is increased until she is quiet. Not more than 1000 ml. of 20 per cent dextrose and 300 mgm. of Pethidine are given in twenty-four hours. 50 mgm. of Diparkol and 50 mgm. of Largactil are given intramuscularly alternately every 4 hours for 48 hours. Thus the sedation is continued for 48 hours. If the fits cannot be controlled within 8-10 hours of treatment and the patient is not in labour, the cervix is closed and uneffaced and the head unengaged, lower segment caesarean section is done under local anaesthesia. If, however, the cervix is effaced and head is engaged, artificial rupture of membranes is done and the second stage of labour cut short by outlet forceps if necessary.

On these lines from July 1955 to October 1958, 402 cases of eclampsia have been treated. Nine mothers were lost, a mortality rate of 2.2%, the lowest ever we had so far. 12 caesarean sections were done in this series and no mother was lost from the caesarean sections. The following relevant observations are made:

1. In 60% of cases there was satisfactory drop in blood pressure during treatment and before delivery.
2. In 95% of cases good urinary output was maintained.
3. The incidence of recurrence of fits in the series of 402 cases was 15%. It is observed that frequent changes of medical and nursing staff is accompanied by an increasing incidence of recurrence of fits. Also if at least 3-4 hours of interval is obtained prior to the start of labour the recurrence of fits will be still less.
4. The incidence of pulmonary complications is reduced to a minimum. In a series of 174 deaths in eclampsia, 40% had pulmonary complications and 29.5% pulmonary oedema. In this series only 5 patients had pulmonary oedema.
5. Hyperpyrexia: In 25.3% of fatal cases referred to previously hyperpyrexia was found as a terminal event. In this series only three cases had hyperpyrexia.
6. Minimum incidence of post-eclamptic psychosis.
7. Absence of shock even in those delivered by caesarean section.

To assess the value of any line of treatment for eclampsia and to make a comparative study with other lines of treatment, I have always maintained that comparable cases should be taken into consideration. All of us will agree that eclampsia varies in severity. We will I think also agree that in the mild cases where the patient comes under treatment soon after a fit or develops eclampsia while under treatment for pre-eclampsia, any of the ordinary sedative lines of management will give good results. It is the really severe cases that test the value of any line of treatment. Hence it is that criteria suggested by the London Committee to classify eclampsia into mild and severe, to compare the different lines of treatment and to assess the prognosis, become so useful. Based on that I give below in Table V the details of the 402 cases treated by this method after separating them into the severe and mild groups.

I repeat that unless similar types of cases are taken into consideration in assessing the comparative merits

TABLE V

Type	Ante-partum and intra-partum	Post-partum	Blood pressure			Average no. of fits before treatment	% of recurrence	Urinary output		Results	
			Highest	Lowest	Average			Good	Poor	Mother	Child
											Perinatal loss
Severe	260	30	240/160	160/120	190/130	13.6	19.6	286	10	2.7%	32.1%
Mild	67	39	180/120	130/90	160/110	5.8	0.8	106	—	I.D.	18.6%

of different types of therapy, wrong impressions are likely to be entertained. 106 cases of eclampsia (mild) have been treated in the series with only one death and if these figures only are presented it may not give the correct assessment. It is really the severe types that test any line of treatment and I am happy to state that even in the severe forms the mortality is only 2.7%.

A high foetal loss is accepted in eclampsia due to prematurity, the toxaemia itself and the sedatives used. In severe cases the perinatal mortality has been 32.1%.

I conclude that the combination of Chlorpromazine, Diethazine and Pethidine constitute a form of conservative therapy which is reasonably effective in the control of convulsions. It has also the added advantages that pulmonary complications, hyperpyrexia, renal failure and shock which enhance the mortality rate in eclampsia are reduced to the minimum and hence the maternal death rate is lowered. However, I believe that if within a reasonable time the convulsions cannot be controlled by this treatment caesarean section in those cases where response to induction may not be favourable or artificial rupture of membranes in the rest could supplement with advantage the conservative regime. Based on these lines 402 cases of eclampsia were treated from July 1955 to October 1958 with a maternal mortality rate of 2.2% the lowest so far on our record.

References

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