

Comparison of Efficacy of Oral and Intravenous Anti-Hypertensive Drugs in Eclampsia- A Randomized Trial

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ABSTRACT

BACKGROUND

Eclampsia increases the risk for both mother and foetus. The treatment aims to quickly bring about smooth reduction in blood pressure to levels that are safe for both, but avoiding any sudden drops, that may in themselves cause dizziness or foetal distress. Hence, this study was conducted to compare the efficacy of anti-hypertensive drugs in eclampsia.

METHODS

80 eclampsia patients were randomized into two groups: one received oral nifedipine and other intra-venous labetalol. Nifedipine group orally received 10 mg initially with repeated doses of 20 mg every 20 minutes up to maximum of 5 doses or until the therapeutic goal was reached. The other group received intravenous labetalol 20 mg initially followed by escalating doses of 40, 80, 80, and then 80 mg every 20 minutes until therapeutic goal was achieved or for a maximum of 5 doses. Once the therapeutic goal was reached, blood pressure was measured every 20 minutes till delivery.

RESULTS

Mean time required to reach therapeutic blood pressure goal in nifedipine, and labetalol group was 45 ± 22.98 and 59.5 ± 25.41 minutes respectively. Total dose requirement was 1.65 ± 0.57 and 2.17 ± 0.74 mg respectively. The differences between two groups were significant. There was difference in urine output between the two groups as well. In the initial two hours, there was increased urine output in nifedipine group though it was statistically not significant. After two hours till 48 hours, this increased urine output in the nifedipine group was significant (p value 0.001).

CONCLUSIONS

nifedipine achieved the therapeutic blood pressure goal more rapidly than labetalol.

KEY WORDS

Eclampsia, Nifedipine, Labetalol, Hypertension

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BACKGROUND

Pre-eclampsia complicated by generalized tonic-clonic convulsion is termed eclampsia. Once eclampsia has ensued, the risk of both mother and foetus is appreciable. Cerebrovascular accident and pulmonary oedema remain important causes of death in eclampsia. There is now compelling evidence in favour of magnesium sulphate, rather than diazepam or phenytoin, for the treatment of eclampsia.¹ So, far as anti-hypertensive is concerned, there is no general consensus on which drug to be used. There is a general consensus that a woman should receive antihypertensive drugs to lower her blood pressure if the systolic blood pressure reaches 170 mm of mercury and/or diastolic blood pressure reaches 110 mm of mercury and she should be in hospital. The aim of treatment is to quickly bring about smooth reduction in blood pressure to levels that are safe for both mother and baby, but avoiding any sudden drops, that may in themselves cause problem such as dizziness or foetal distress. Until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug, and on what is known about adverse effects. Exceptions are Diazoxide, Ketanserin, Nimodipine and Magnesium sulphate, which are probably best avoided.²

The Cochrane Review suggests that well-designed large trials are needed to make reliable comparison of the maternal, foetal, and neonatal effects of antihypertensive in common clinical practice. Ideally clinician should compare an agent they are familiar with in their routine clinical practice with a promising alternative that is available locally, or would be likely to become if shown to be preferable.² In our hospital we are using oral nifedipine and intravenous/oral labetalol in patients with severe pre-eclampsia. We are also using sublingual nifedipine in some cases of eclampsia who cannot take orally. Hence, the study conducted aimed to compare the efficacy of anti-hypertensive drugs-oral (sublingual if, she cannot take orally) nifedipine and intravenous labetalol in eclampsia. The primary objective was to evaluate the time to achievement of therapeutic goal. (therapeutic goal is Systolic Blood pressure of <160 mm of mercury and diastolic BP of < 100 mm of mercury) by oral (sublingual in cases who cannot take orally) nifedipine versus intravenous (orally when she is in a position to take) labetalol. The secondary objective was to compare the secondary outcome variable -Agent failure; urinary output; Maternal adverse outcome (headache, flushing, nausea, renal failure, pulmonary oedema, respiratory depression, hepatic failure, abnormalities in clotting system, stroke, recurrent convulsion, length of stay and maternal death; foetal outcome (foetal heart rate abnormality, 5 minutes Apgar score less than 7, N.I.C.U. admission and still born).

METHODS

Patients were enrolled (n=87); out of which 80 fulfilled the inclusion criteria. A single blind parallel group randomized study design was used. Randomization was done by computer generated random number list. Patients blinding to the type of antihypertensive given did not matter in this

study because all the patients of eclampsia get admitted in a state of mental confusion. Though the doctor who gave the drug knew which antihypertensive was given to the patient, but the blood pressure was measured by another doctor thereby the assessor was kept blind. Allocation concealment was done by opaque sealed envelope which was prepared by a person not involved in the study. 80 patients were again randomized divided into two groups after obtaining the filled informed consent.

The study commenced after the approval of the institutional ethics committee. 40 patients received oral nifedipine and remaining 40 received intravenous labetalol. All eclampsia patients with gestational age more than 24 weeks (antepartum, intrapartum and postpartum within 24 hours of delivery) and age ranging less than 45 years were included in this study. Women with known atrio-ventricular heart block, moderate to severe bronchial asthma, exposure to either of the study drugs in 24 hours of enrolment were excluded. Patient randomized to nifedipine received orally 10 mg of drug initially with repeated dose of 20 mg in every 20 minutes and up to maximum of 5 doses or until the therapeutic goal was reached. For unconscious patients nifedipine was given sublingually (by puncturing nifedipine capsule and placing it beneath the tongue).

Patients suitable for oral administration were instructed to swallow the capsule (oral nifedipine capsule). Patient randomized to intravenous labetalol received 20 mg initially followed by escalating doses of 40 mg, 80 mg, 80 mg and then 80 mg every 20 minutes until the therapeutic goal was achieved or for a maximum of 5 doses. The dosing regimen for each study medication corresponded with the regimen from two previous clinical trial.^{3,4} Whenever patient was in a state to swallow the tablet, labetalol was given as oral tablet. Randomization was done by computer generated random number list. Patients blinding to the type of antihypertensive given was not of significance to the study because all the patients of eclampsia got admitted in a state of mental confusion.

Albeit the doctor who administered the drug was aware of the type of antihypertensive given, the blood pressure was recorded by another doctor thereby it was ensured the assessor was blinded. Allocation concealment was done by opaque sealed envelope which was prepared by personnel not involved in the study. The following parameters are studied: Maternal- number of convulsion with time, complaining of headache, flushing, nausea, level of consciousness, systolic and diastolic blood pressure, urine output, respiratory system examination, cardio-vascular system examination, mode of delivery, time of delivery, time interval between initiation of therapy & delivery. foetal parameters were: foetal heart rate abnormalities, Apgar score at 5 minutes, N.I.C.U. admission and still born. Urine output volume was collected and recorded with a Foley's catheter and graduated urobag for 48 hours after initial dosing. Continuous foetal heart rate monitoring was done of all undelivered patient and any maternal side effect or foetal heart rate abnormalities were recorded.

Additional neonatal outcome was evaluated including 5 minutes Apgar score and N.I.C.U. admission. Once the therapeutic goal was reached blood pressure was measured every 20 minutes till delivery. After delivery blood pressure was measured every half an hour for the first day and every

fourth hourly for the remaining days of her stay in the hospital. As all the patients reached the therapeutic blood pressure goal within five doses so cross over was not required. Blood was sent for estimation of platelet count, liver function test, urea, creatinine, urine analysis, were done during admission and at an interval of 4 hours.

Statistical Analysis

Numerical data was analysed by using Student unpaired t – test, categorical data was analysed by Fisher exact test or Chi square test which ever applicable. P value of <0.05 was considered to be statistically significant.

RESULTS

The baseline characteristics of patients of nifedipine and labetalol groups were comparable. There was no difference between the two groups regarding the mode of delivery & time interval between starting antihypertensive drug and time of delivery (table 1). The time and number of doses required to reach therapeutic goal between the two groups was significant (table 2). There was difference in urine output between nifedipine and labetalol groups. In the initial two hours, there was increased urine output in nifedipine group though it was statistically not significant. After two hours till 48 hours, this increased urine output in the nifedipine group was significant (table 3).

The maternal adverse outcome like headache, nausea, flushing, cerebro-vascular accident, renal failure, pulmonary oedema and jaundice were similar in both nifedipine and labetalol group. There was no maternal death in either groups (table 4). foetal heart rate abnormality, Apgar score at 5 minutes <7, NICU admission were similar in both nifedipine and labetalol group. There was one stillborn in nifedipine group where patient had received nifedipine by sublingual route because she was unconscious. There was no history of stillborn out of the 7 post-partum eclamptic patients (Table 5).

Mode of Delivery	Nifedipine n=40	Labetalol n=40	P†
V.D.	9(22.5%)	7(17.5%)	0.577†
Forceps	1(2.5%)	4(10%)	0.205†
Caesarean section	30(75%)	29(72.5%)	0.799†
Time interval between starting antihypertensive drug and time of delivery			
Time interval between starting antihypertensive drug and time of delivery	5.23 ± 2.81 (mean ± S.D.)	4.71 ± 2.39 (mean ± S.D.)	0.375*
Time interval between starting antihypertensive drug and time of vaginal delivery	4.54 ± 2.73 (mean ± S.D.)	5.5 ± 3.38 (mean ± S.D.)	0.485*

Table 1. Mode of Delivery & Time Interval between Starting Antihypertensive Drug and Time of Delivery

†Chi-square test *Student unpaired t-test

Variable	Nifedipine n=40 Mean ± S.D.	Labetalol n=40 Mean ± S.D.	P (Student unpaired t-test)	95% C.I.
Time (min) taken to reach therapeutic goal	45 ± 22.98	59.5 ± 25.41	0.0091	3.71-25.28
Number of doses required to reach therapeutic goal	1.65 ± 0.57	2.17 ± 0.74	0.0007	0.22-0.81

Table 2. Time and No. of Doses Required to Reach Therapeutic Goal

Duration (h)	Nifedipine (ml)	Labetalol (ml)	P (Student Unpaired t-Test)	95% C.I.
1	119.5 ± 74.28	108.6 ± 87.57	0.550	25.24-47.04
2	213.6 ± 102.33	183.88 ± 117.57	0.231	19.34-78.78
6	560 ± 153.67	455.55 ± 144.8	0.002	37.98-170.91
12	1045 ± 257.65	863.88 ± 258.18	0.002	66.30-295.93
18	1597.5 ± 407.92	1265.27 ± 328.15	0.0001	167.43-497.02
24	2142 ± 509.34	1731.94 ± 372.02	0.0001	211.51-608.60
48	2997.5 ± 647.47	2483.33 ± 408.83	0.0001	273.13-755.21

Table 3. Urine Output

	Nifedipine (n=40)	Labetalol (n=40)	Relative risk	95% C.I.	P*
Headache	14(35%)	7(18.5%)	2.00	0.903-4.426	0.08
Nausea	8(20%)	6(15%)	1.33	0.50-3.49	0.558
Flushing	9(22.5%)	4(10%)	2.25	0.754-6.713	0.146
CVA	1(2.5%)	0	3.00	0.125-71.51	0.497
Renal failure	2(5%)	5(12.5%)	0.4	0.082-1.942	0.255
Pulmonary Oedema	0	3(7.5%)	0.14	0.007-2.679	0.19
jaundice	2(5%)	1(2.5%)	2.00	0.188-21.18	0.564

Table 4. Adverse Maternal Outcome

*Chi-square test

	Nifedipine† n=36	Labetalol ‡ n=37	R.R.	95% C.I.	P*
Foetal heart rate abnormality	4(11.1%)	5(13.5%)	0.82	0.239-2.819	0.755
Apgar score at 5 min <7	10(27.7%)	11(29.7%)	0.93	0.453-1.925	0.854
NICU admission	10(27.7%)	11(29.7%)	0.93	0.453-1.925	0.854
Stillborn	1(2.7%)	0(0)	3.08	0.129-73.24	0.486

Table 5. Adverse Infant Outcome

*Chi-square test
†Nifedipine group -4 post-partum eclampsia
‡Labetalol group- 3 post-partum eclampsia

DISCUSSION

In this study, nifedipine achieved the therapeutic blood pressure goal more rapidly than labetalol. The numbers of doses required were also significantly less in the nifedipine group as compared to the labetalol group. These results were similar to the result by Vermillion et al.⁵

In this study patient receiving nifedipine experienced a significant increase in urine output compared with the women receiving labetalol. Within first two hours though the increase was not significant, but after that till forty-eight hours there was significant increase. In a study by Vermillion et al,⁵ they have found significant increase in urine output in patient receiving nifedipine as early as one hour after initial dosing. Because the pathogenesis of pre-eclampsia and eclampsia predisposes the patients to intra-vascular volume depletion and decreased renal perfusion, nifedipine ability to increase renal perfusion and urinary output in the context of pre-eclampsia and eclampsia would appear to be beneficial. The ability of nifedipine to enhance urine output has been attributed to a selective renal arteriolar vasodilatation and has also been reported in randomized controlled trials involving post-partum pre-eclamptic patients⁶ and in chronic hypertensive patients after renal transplantation.⁷

The potential for the tocolytic effect of nifedipine in those intrapartum patients attempting a vaginal delivery could theoretically prolonged labour. This was not specifically

evaluated in our study because ten out of forty patients delivered vaginally of which one patient required outlet forceps. Out of forty patients receiving labetalol eleven delivered vaginally of which outlet forceps were applied in four cases. All the five cases of outlet forceps including both groups had foetal distress as their indication. Most of patients receiving nifedipine required only one or two doses to achieve the therapeutic goal. Therefore, these patients were exposed to smaller concentration of nifedipine than those used acutely in the tocolytics trials evaluating nifedipine.^{8,9} So far as maternal adverse outcome concerned minor side effects like headache, nausea and cutaneous flushing were comparable in both the groups. Incidence of major maternal adverse outcome like cerebro-vascular accident, renal failure, pulmonary oedema and jaundice were also similar in both the groups. There was only one case of cerebro-vascular accident in the whole study which was in the nifedipine group. There were three cases of pulmonary oedema in the labetalol group and none in the nifedipine group.

There was no significant difference in foetal adverse outcome like intra-uterine foetal heart rate abnormality, Apgar score at 5 min <7, NICU admission in both the groups. There was only one stillborn in the nifedipine group who had received sublingual nifedipine because of her unconsciousness. This patient had overshoot hypotension after giving sublingual nifedipine which resulted in severe foetal bradycardia and resulted in stillborn baby though the baby was delivered by caesarean section immediately after severe bradycardia.

There were three unconscious patients in the nifedipine group and one in labetalol group. These three patients in the nifedipine group were not in a state to take oral drugs. So, sublingual nifedipine were given in these three patients. Out of the three, one had overshoot hypotension resulting in a fresh still-birth. This is one of the important limitations of our study. Minor maternal adverse outcome like headache and nausea has been compared in our study as adverse effect of the two drugs but in reality, it may be due to the disease process itself.

At the beginning of the study it was known to us that we might get some unconscious patients of eclampsia who will not be in a state to take nifedipine orally and we might have to give it sublingual with adverse effect. Still we have done the study as injection labetalol is a costly drug and many of our patients may not be able to afford it.

This study does not have external validity because most of the patients in our study are from low socio-economic status and none from upper class. The result of our study is not generalizable to all strata of the patients in our study. There should be long-term follow up to assess possible effects on the woman's risk of cardiovascular problems after discharge from hospital, and on growth and development of the child. This is relevant not only because these drugs may cross the placenta, but also because too rapid lowering of blood pressure with a placenta that has marginal functional reserve could lead to ischemic brain injury and long-term neurodevelopment problems.

Alongside data from randomized trials, mechanisms need to be developed to monitor possible rare adverse events related to in utero exposure to antihypertensive agents.

CONCLUSIONS

Nifedipine achieved the therapeutic blood pressure goal more rapidly with significantly smaller number of required doses as compared to the labetalol group. Patients receiving nifedipine experienced a significant increase in urine output when compared to women receiving labetalol. There was no significant difference in foetal adverse outcome like intra-uterine foetal heart rate abnormality, Apgar score at 5 min <7, and NICU admission in both the groups. There was no significant difference in major maternal adverse outcome or foetal adverse outcome in both the groups.

Most of the patients belonged to low socio-economic status and none from upper class; hence, results cannot be generalizable to all strata of the patients.

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