# Use of midazolam as a 1st line anticonvulsant in neonatal seizures

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# What anticonvulsant as first line?

Phenobaritone/phenytoin

or

Midazolam

# Efficacy of Phenobarbitone/ Phenytoin

- Phenobarbitone and Phenytoin, were introduced as anticonvulsants in 1914 and 1938
- Neonatal seizure is refractory to Phenobarbitone/Phenytoin in >50% cases*
- Long acting (half life>120 hours)
- Delay recovery
- Long term use affects neurodevelopment and cognitive function

*Source: Sirsi D, Nangia S, LaMothe J, Kosofsky BE, Solomon GE. 2008

# Cont....

- **Neonatal seizures**

  **After all these years we still love what doesn't work [1]**

- **Phenobarbital for Neonatal Seizures: A Time for Perusal [2]**

[1]Sankar R, Painter MJ. Neonatal seizures: after all these years we still love what doesn't work. Neurology. 2005 Mar 8;64(5):776-7. PubMed PMID: 15753407.

[2] Jain P, Sankhyan N. Phenobarbital for Neonatal Seizures: A Time for Perusal. Indian Pediatr. 2016 May 8;53(5):381-2. PubMed PMID: 27254043.

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# Midazolam

- Approved for clinical use in 1976
- Short acting benzodiazepine
- Considered a safe and effective anti-epileptic drug in refractory neonatal seizures

# Objective

To compare the effectiveness and safety of Phenobarbitone and Midazolam as a first line drug in the treatment of neonatal seizures

# Methods

- ***Study Design***

  Randomised Control Trial

- **Study period**

  October 2014 to October 2016

- **Place of Study**

  Paediatrics Department

  Centre for Woman and Child Health (CWCH)

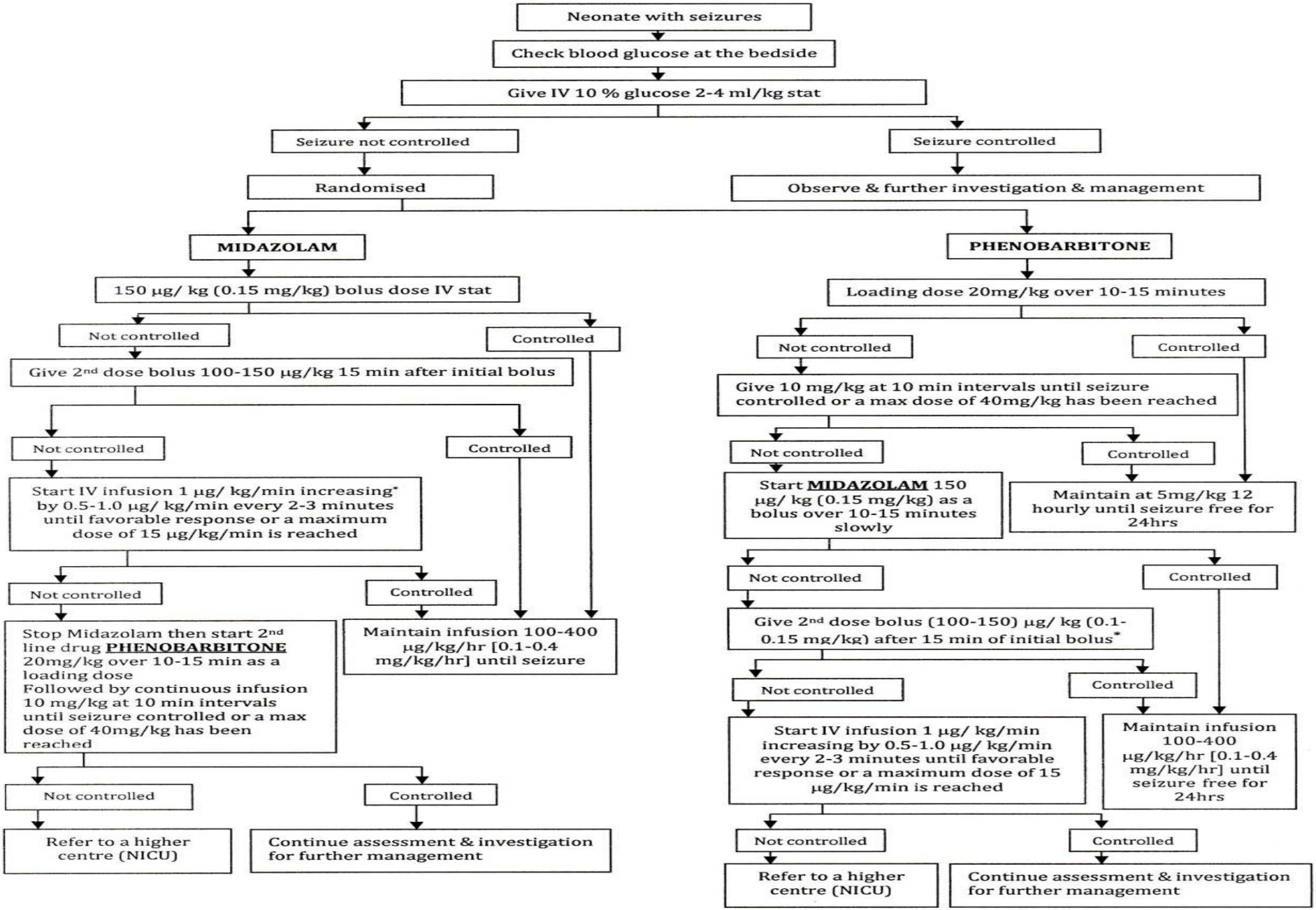
- **Study population**

  Neonates (0-28 days)

# Cont….

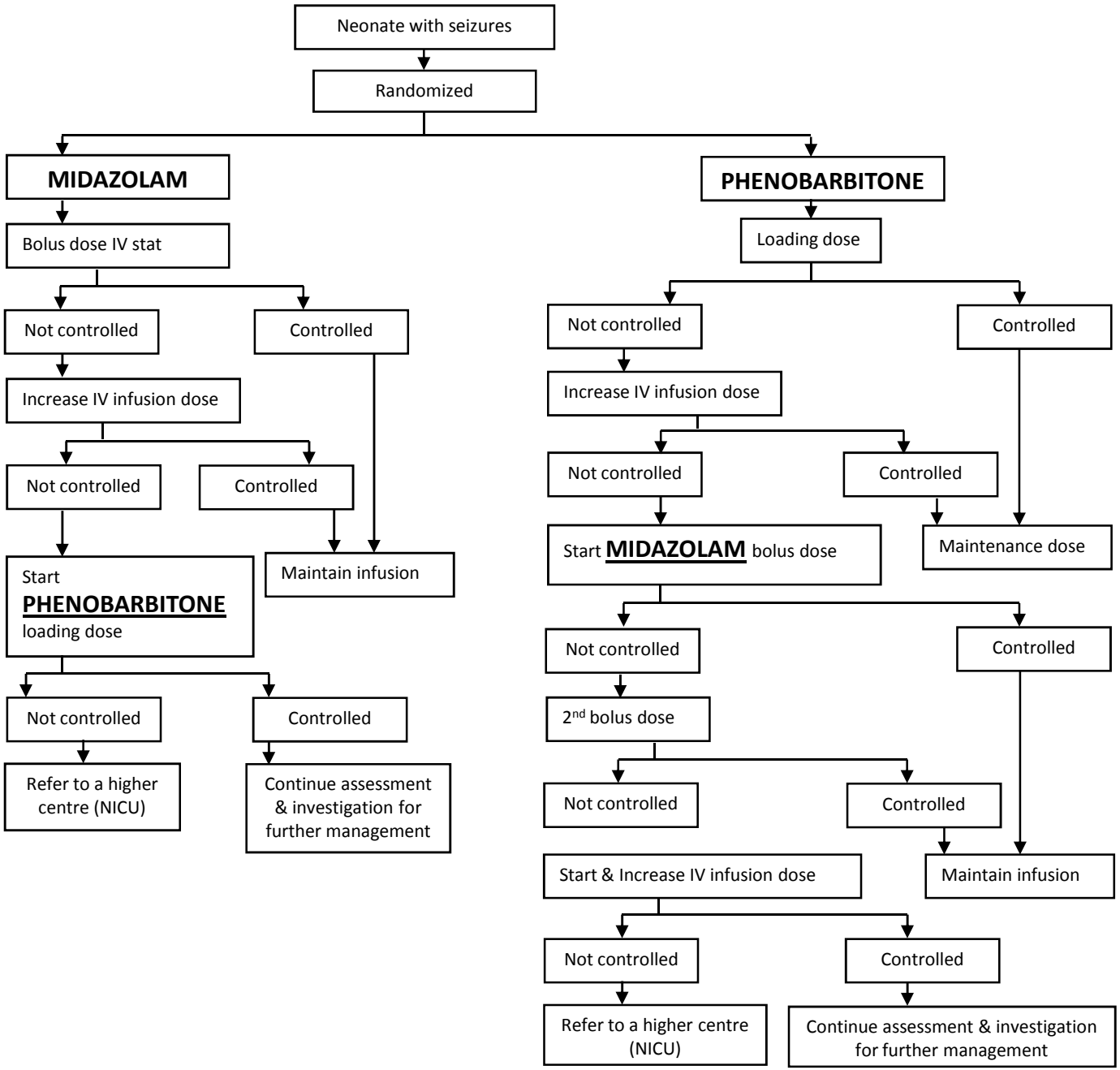
- Approved by Ethical Committee of CWCH
- Written consent taken from parents
- Group A for Phenobarbitone (Control group)
- Group B for Midazolam (Intervention group)
- Randomisation done by duty nurse who opened a sealed envelope containing a piece of paper with either Phenobarbitone or Midazolam written on it
- Algorithm flow chart followed throughout

**Figure: Flow chart for management of neonatal seizures**

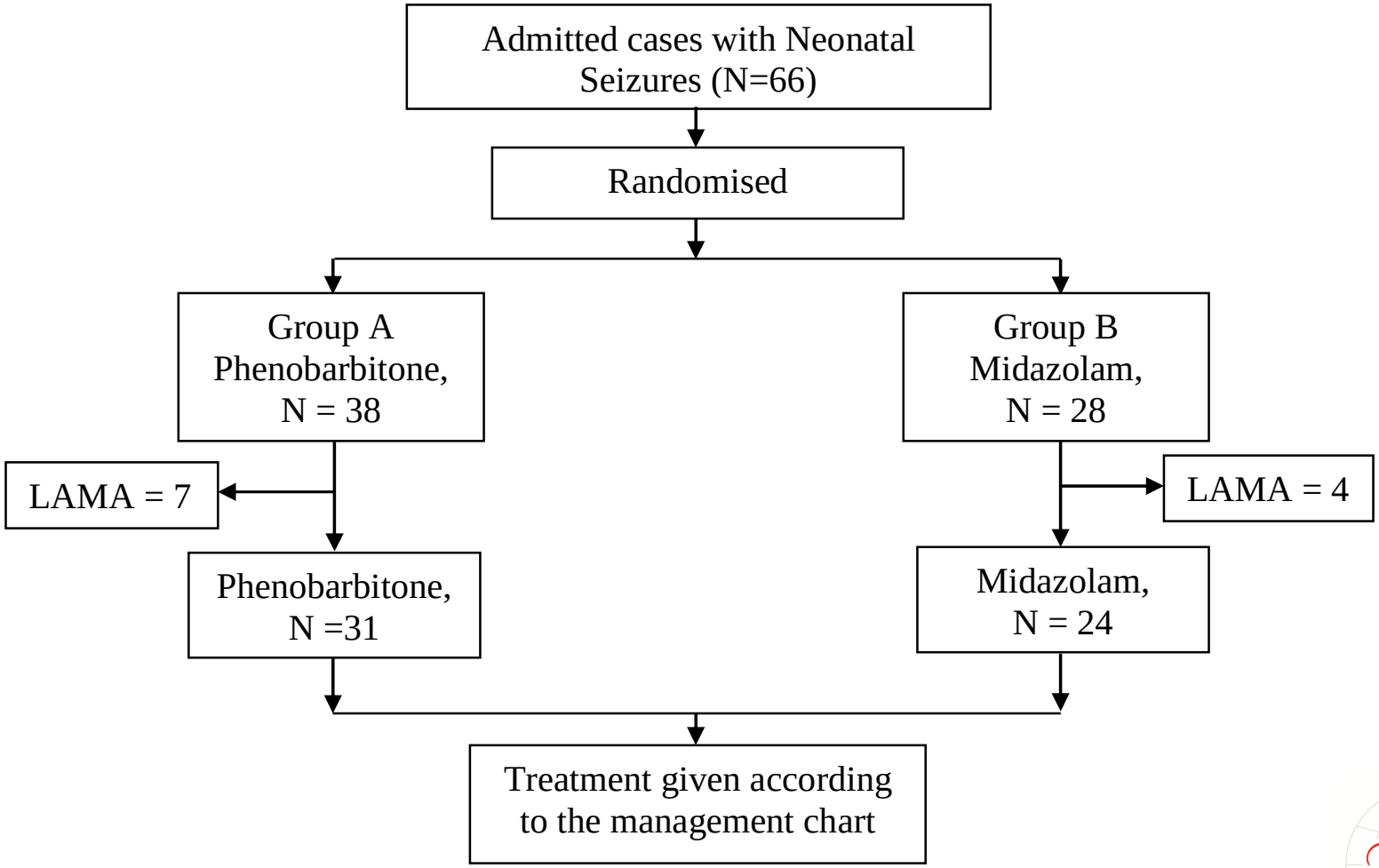



***Midazolam infusion preparation**

Mix Inj.Midazolam 5mg in 50ml 5% or 10% dextros
(1ml contain 0.1mg/ml or 100µg/ml)


Neonate with seizures
Randomized
MIDAZOLAM
Bolus dose IV stat
Not controlled
Controlled
Increase IV infusion dose
Not controlled
Controlled
Start PHENOBARBITONE loading dose
Maintain infusion
Not controlled
Controlled
Refer to a higher centre (NICU)
Continue assessment & investigation for further management
PHENOBARBITONE
Loading dose
Not controlled
Controlled
Increase IV infusion dose
Not controlled
Controlled
Start MIDAZOLAM bolus dose
Maintenance dose
Not controlled
Controlled
2nd bolus dose
Not controlled
Controlled
Start & Increase IV infusion dose
Maintain infusion
Not controlled
Controlled
Refer to a higher centre (NICU)
Continue assessment & investigation for further management

# Flow chart of patient allocation and analysis



# Results

# Table I: Comparison of demographic characteristics between Control and intervention groups

| | **Control group (Phenobarbitone)** ***N=31 (%)*** | **Intervention group (Midazolam)** ***N=24 (%)*** | ***P value*** |
|---|---|---|---|
| Gender | | | |
| Male | 19 (61) | 17 (71) | |
| Female | 12 (39) | 7 (29) | 0.57 |
| Mode of delivery | | | |
| Normal | 26 (84) | 20 (83) | |
| Caesarean | 5 (16) | 4 (17) | 1.00 |
| Place of delivery | | | |
| CWCH | 6 (19) | 3 (12.5) | |
| Home | 17 (55) | 12 (50) | 0.31 |
| Other facilities | 8 (26) | 9 (37.5) | |

# Table II: Underlying causes of neonatal seizures

| | **Control group (Phenobarbitone)** ***N=31 (%)*** | **Intervention group (Midazolam)** ***N=24 (%)*** | ***P value*** |
|---|---|---|---|
| Hypoxic ischaemic encephalopathy stage II | 20 (64.5) | 21 (87.5) | 0.06 |
| Neonatal sepsis / Meningitis | 7 (23) | 3 (12.5) | 0.48 |
| Hypoglycemia | 1 (3.2) | 0 (0) | 1.00 |
| Hyponatraemia | 1 (3.2) | 0 (0) | 1.00 |

# Table III: Comparison of clinical features between control and intervention groups

| | **Control group (Phenobarbitone)** ***N=31 (%)*** | **Intervention group (Midazolam)** ***N=24 (%)*** | ***P value*** |
|---|---|---|---|
| Admission weight | | | |
| <2500 g | 7 (23) | 8 (33) | 0.54 |
| ≥2500 g | 24 (77) | 16 (67) | |
| Age at admission | | | |
| Within 72 h | 17 (55) | 18 (75) | 0.16 |
| (2-28) d | 14 (45) | 6 (25) | |
| Type of neonatal convulsion | | | |
| Subtle | 17 (55) | 17 (71) | |
| Tonic - clonic | 13 (42) | 7 (29) | 0.18 |
| Myoclonic | 1 (3.2) | 0 (0.0) | |

# Cont……

| | **Control group (Phenobarbitone)** ***N=31 (%)*** | **Intervention group (Midazolam)** ***N=24 (%)*** | ***P value*** |
|---|---|---|---|
| Oxygen saturation (≤ 95%) | 11 (79) | 7 (64) | 0.65 |
| Cycling limbs | 10 (32) | 11 (46) | 0.40 |
| Tonic - clonic | 11 (35.5) | 7 (29) | 0.77 |
| Oral-facial lingual | 6 (19) | 8 (33) | 0.35 |
| Ocular | 3 (9.7) | 1 (4.2) | 0.62 |
| Myoclonic | 2 (6.5) | 0 (0) | 0.49 |
| Aponea | 1 (3.2) | 0 (0) | 1.00 |
| Autonomic tachycardia | 0 (0) | 1 (4.2) | 0.43 |

# Table IV: Treatment outcome between two anticonvulsants

| | **Control group (Phenobarbitone)** ***N=31 (%)*** | **Intervention group (Midazolam)** ***N=24 (%)*** | **P value** |
|---|---|---|---|
| 2nd line drug required | 13 (42) | 2 (8.3) | 0.006 |

# Table V: Adverse effects of anticonvulsants

| | **Control group (Phenobarbitone)** ***N=31 (%)*** | **Intervention group (Midazolam)** ***N=24 (%)*** | ***P value*** |
|---|---|---|---|
| Aponea within 20 minutes | 2 (6.5) | 2 (8.3) | 1.00 |
| Urinary retention | 2 (6.5) | 1 (4.2) | 1.00 |

# Conclusions

Midazolam is more effective as a first line drug in controlling neonatal seizures and that it is as safe as Phenobarbitone in this age group

# References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Thank You

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