National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Obstetrics - hypertension

Date: 06 May 2015

Medication: Labetalol 100mg orally

Indication: Hypertension in pregnancy

Executive summary: International guidelines[1, 2] recommend the use of antihypertensive in the treatment of hypertension in pregnancy. Although there is consensus internationally that anti-hypertensive treatments such as methyldopda, nifedipine and labetalol is safe it is unclear which anti-hypertensive is most effective. A Medline (Pubmed) search was conducted to synthesize evidence for the comparison of oral labetalol with methyldopa and other anti- hypertensive agents in the treatment of chronic hypertension, and severe hypertension. Labetalol, although used as first-line treatment have not shown any benefit over existing anti-hypertensive agents used in the treatment of hypertension in pregnancy.

Introduction: Mild to moderate hypertension is common in pregnancy and sometimes can progress to pre-eclampsia and possible premature delivery. Anti-hypertensive medicines are used to prevent progression to pre-eclampsia. Although there are no consensus on the treatment of mild to moderate hypertension, internationally it is agreed that methyldopa, long acting nifedipine and labetalol orally as acceptable treatment of mild to moderate hypertension in pregnancy and that severe hypertension in pregnancy is treated with short acting antihypertensive such as hydralazine and labetalol intravenously.

Currently in South Africa, in accordance with the EDL Hospital Level standard treatment guidelines, chronic hypertension is treated with methyldopa and severe hypertension in pre-eclampsia is treated with methyldopa and/or amlodipine and/or hydralazine depending on the blood pressure treatment response. In hypertensive emergencies oral short acting nifedipine and labetalol intravenously are used.

Internationally:

- United Kingdom uses labetalol as first line treatment of moderate to severe hypertension with methyldopa and nifedipine as alternatives.
- Australia uses methyldopa and labetalol as first line, and nifedipine and hydralazine as second line.
- Canada uses nifedipine, methyldopa hydralazine and labetalol as treatment options for hypertension in pregnancies.

The information below is extracted from the UK Guidelines on treatment of hypertension in pregnancy.

Labetalol[1] is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPC (August 2013) advises that it should only be used during the first trimester of pregnancy if the potential benefit outweighs the

potential risk, and that breastfeeding is not recommended. Informed consent on the use of labetalol in these situations should be obtained and documented.

Methyldopa[1] is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 2013) advises that its use in women who are, or may become, pregnant or who are breastfeeding their newborn infant requires that anticipated benefits be weighed against possible risks. Informed consent on the use of methyldopa in these situations should be obtained and documented.

Nifedipine[1] is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 2013) advises that it is contraindicated in women who may become pregnant, and in pregnancy before week 20, and that any use in pregnancy after week 20 requires a very careful individual risk benefit assessment. It also advises that nifedipine should not be used during breastfeeding. Informed consent on the use of nifedipine in these situations should be obtained and documented.

Similarly in South Africa, the three agents, Nifedipine, methyldopa and labetalol are registered accordingly.

With the shortage of methyldopa, long-acting nifedipine not available on contract and reluctance of clinicians to use amlodipine (for which there is insufficient evidence of the use in pregnancy), treatment of hypertension in pregnancy is currently a challenge to clinicians.

Search strategy:

The following search strategies were employed:

PUBMED search terms:

1. *Labetalol and methyldopa randomized controlled trials*

Randomized controlled trial[pt] AND labetalol[tiab] AND pregnancy[tiab] AND methyldopa[tiab]

2. *Labetalol in systematic reviews*

("labetalol"[MeSH Terms] OR "labetalol"[All Fields] OR "labetalol"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND intravenous[All Fields] AND ("Pregnancy Hypertens"[Journal] OR ("pregnancy"[All Fields] AND "hypertension"[All Fields]) OR "pregnancy hypertension"[All Fields]) AND "Systematic Review"[All Fields]

Selection of studies:

Types of studies: randomized controlled trials and systematic reviews

Participants: Women with mild to moderate hypertension to severe hypertension

Intervention: Oral Labetalol

Comparators: Methyldopa, nifedipine,

Outcomes: severe hypertension, pre-eclampsia, any reported death, preterm births and small gestational age.

Evidence synthesis:

There were limited good-quality trials to evaluate the effectiveness of labetalol and methyldopa for treatment of chronic hypertension during pregnancy.

In on RCT 300 women with mild chronic hypertension were randomized at 6-13 weeks pregnant were randomized to methyldopa, labetalol or controlled group[3]. Patients treated with methyldopa and labetalol had significantly lower blood pressure than the control group[3]. However, there was no difference amongst the group with regards to incidence of pre-eclampsia. Women in the in the methyldopa group ((OR 1.21; 95% CI 0.55 to 2.65) and the labetalol group (OR 1.06; 95% CI 0.47 to 2.37) were as likely to develop pre-eclampsia as the no-treatment group. All three treatment groups did not require additional drugs for the treatment of chronic hypertension before 37 weeks.

A low quality study investigated labetalol vs methyldopa in which 19 patients were given either labetalol or methyldopa [4]. However this study did not reveal any statistical significant differences between labetalol and methyldopa.

A RCT assessing the perinatal efficacy and perinatal safety of labetalol in the treatment of hypertension in pregnancy showed that labetalol may be as safe as methyldopa in the treatment of hypertension.[5]

Firoz et.al (2014) systematically reviewed the effectiveness of oral anti-hypertensive agents for severe and post-partum hypertension which included fifteen RCTs in pregnancy and one past-partum triral[6]. Only one single trial inclluded in this systematic review compared oral labetalol 100mg four times daily with methyldopa 250mg 4 times daily. The anti-hypertensive agents showed no difference in achievement of target blood pressure (47%and 56% RR=0.85 CI (0.54-1.33).No difference in rate of caesarian delivery (50% vs 59% RR= 0.85 CI 0.56-1.33) or perinatal deaths 5% vs 0%; RD= 0, 05 95% CI 0.03- 0.14)

Another low quality trial randomized controlled trail assessed the efficacy and safety of labetalol vs methyldopa in the management of mild to moderate pregnancy induced hyperetension[7].Labetalol shown quicker and more efficient blood pressure control. However there was no evidence of this in the report. Also there was no difference in the mean duration of pregnancy and neonatal outcome between the two groups.

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Evidence quality:

Assessment of the quality of trails included concealment, attrition bias, and performance bias. The quality of the body of evidence range from very- low to moderate (in terms of GRADE) and as a result the confidence in the estimates provided in these studies may likely be seen as biased estimates of the effect of labetalol. Only one trial of moderate quality was found.

The systematic review, included only one trial that assessed labetalol compared to methyldopa and hence the relevance of this systematic review on the comparison of labetalol and methyldopa is indirect. The systematic review indicated that a head to head comparison of oral agent's labetalol, nifedipine and methyldopa is required to inform decisions on which agent to include.

Alternative agents: methyldopa and nifedipine

Summary:
Considering the evidence from the trials and systematic review does not make it possible to ascertain which antihypertensive agent, methyldopa or labetalol is ideal for the treatment of hypertension in pregnancy. The results of these trials do show that anti-hypertensive treatment does reduce the risk of severe hypertension. Large simple trials that estimates the benefits of labetalol compared to methyldopa and nifedipine are required to ascertain the preferred anti-hypertensive agent in pregnancy. One such trail is underway.

Recommendation:
There is insufficient evidence that labetalol is better than methyldopa and vice versa. The choice should depend on previous experience and familiarity with the anti-hypertensive agent. Further evidence is required to inform decision to include labetalol or remove methyldopa. Methyldopa still remains preferred agent.
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References

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