Original Article

Comparative evaluation of efficacy and safety of methyldopa and labetalol in pregnancy-induced hypertension: A meta-analysis

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ABSTRACT

Introduction: Methyldopa and labetalol are the drugs that frequently used for the management of pregnancy-induced hypertension. But fewer data available for the efficacy and safety of their use. So, here we are doing a systemic review for the safety and efficacy of methyldopa in comparison to labetalol.

Objectives: Assessment of efficacy and safety of methyldopa versus labetalol in pregnancy-induced hypertension.

Method: A total of 10 randomized controlled trials (RCTs) following PRISMA guidelines (2015) and have included pregnant women who developed hypertension after the 20th week of gestation and receiving methyldopa (100–400 mg/day) or labetalol (250–1000 mg/day). All RCTs with changes in mean arterial pressure (MAP) before and after drug administration was collected. The adverse effects of the respective drugs were also noted. RevMan 5.3 software was used for the calculation of standardized mean difference (SMD). *P* value less than 0.05 will be considered significant.

Result: Data of 1,200 patients were included in our study. Both the drug decreases MAP statistically significantly. In the labetalol group, *P* value was statistically significant (random effect model $P < 0.005$ and in the fixed-effect model <0.001). In methyldopa group, $P < 0.001$, significant in fixed effect. In the majority of the studies, the difference in the reduction of MAP was higher in labetalol than methyldopa. In labetalol vs methyldopa study using random-effect model SMD was 1.568 (95% CI, 0.735 to 2.401, $P < 0.001$). Drowsiness, headache, nausea, vomiting, weakness, and myalgia were associated with drugs. Out of the six adverse effects, there was a significant difference found in drowsiness ($P = 0.023$) which was seen more in patients receiving methyldopa. There was no significant difference in the prevalence of the other maternal side effects.

Conclusions: Labetalol is more efficacious and safer as compared to methyldopa.

Key words: Efficacy; labetalol; methyldopa; pregnancy-induced hypertension; safety.

Introduction

Hypertensive disorders are the most common medical complications of pregnancy, affecting 7.8% of all pregnancies in India and account for approximately a quarter of all antenatal admissions.[1] These disorders are responsible for approximately one-third of maternal mortality in India.[2] Despite years of research in this field, there remains a lack of consensus on the classification/definition of hypertensive disorders of pregnancy, the blood pressure at which antihypertensive therapy needs to be initiated, what constitutes an appropriate antihypertensive

Access this article online	
Website: www.tjogonline.com	Quick Response Code
DOI: 10.4103/TJOG.TJOG_87_19	

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How to cite this article: Patel R, Shah R, Lad D, Rana D, Malhotra S. Comparative evaluation of efficacy and safety of methyldopa and labetalol in pregnancy-induced hypertension: A meta-analysis. Trop J Obstet Gynaecol 2020;37:119-25.

Received: 06-09-2019 **Revised:** 25-03-2020
Accepted: 02-04-2020 **Published Online:** 14-08-2020

agent in pregnancy and the maternal-fetal-risk-benefit ratio of treatment.[3] There is evidence that hospitalization early in the course of the disease improves maternal and perinatal outcomes, but the use of antihypertensive drugs in pregnancy-induced hypertension (PIH) is currently under debate.[4,5] This meta-analysis is used to determine and compare the efficacy of treatment with methyldopa vs labetalol with respect to maternal-perinatal benefits and adverse effects.

PIH is the development of new hypertension in a pregnant woman after 20 weeks of gestation along with having blood pressure greater than 140/90 on two separate occasions at least 6 h apart and without the presence of protein in the urine.[6,7] If not treated it leads to a condition known as pre-eclampsia, which is defined as gestational hypertension + proteinuria.[8] In later stages, if tonic-clonic seizures develop along with the above two preexisting conditions, it aggravates to eclampsia.[9] Eclampsia is serious for both mother and baby which can cause a coma in the mother and can be fatal for both.[10] Thus, it is the doctor's utmost priority to treat PIH in its earlier stages.

An array of anti-hypertensive drugs is available out of which methyldopa is the oldest drug giving promising results in treating PIH while Labetalol is a rather unique drug that has shown to be effective in the treatment of essential hypertension while its uses in treating PIH are still being assessed.[11]

Methyldopa is a phenylalanine derivative and an aromatic amino acid decarboxylase inhibitor its anti-hypertensive actions seems to be attributable to its conversion into alpha-methyl norepinephrine, which is a potent alpha-2 adrenergic agonist that binds to and stimulates potent central inhibitory alpha-2 adrenergic receptors. This results in a decrease in sympathetic outflow and decreased blood pressure.[12]

Labetalol is a third-generation selective alpha-1-adrenergic antagonist and nonselective beta-adrenergic antagonist. It competitively binds to alpha-1-adrenergic receptors in vascular smooth muscle, thereby inhibiting the adrenergic stimulation of endothelial cell function and vasoconstriction in peripheral blood vessels. This agent also binds to beta-receptors in the bronchial and vascular smooth muscle, resulting in a decrease in both systolic and diastolic blood pressure.[13]

Methods

This is a meta-analysis between two different drugs used in PIH.

Step 1: Identification and literature search

We identified original randomized controlled trials by an all-language search of all articles (any year up to May 2019) in the Cochrane Controlled Trials Register (CCTR), Medline, Google Scholar, and EMBASE. We subsequently screened the references of all retrieved articles to identify additional relevant publications. The following search strings and MESH terms were used: *"Methyldopa vs Labetalol" OR "Gestational Hypertension treatment AND randomized controlled trial."*

Step 2: Criteria for selection of studies

All study-related randomized controlled trials (RCTs) using either:

- An adequate method of allocation concealment (e.g. sealed opaque envelopes),
- Studies that were double-blind, single-blind, or unblinded,
- Studies that included a comparison of methyldopa with labetalol individuals with PIH.

We included any RCT in pregnant women with gestational hypertension that compared the effects of methyldopa and labetalol on blood pressure and their respective adverse effects.

All RCTs which followed CONSORT (1996) and PRISMA (2015) guidelines were included.

Step 3: RCT enrolment criteria

Inclusion criteria

- All the pregnant women were normotensive before the 20th week of gestation who developed hypertension.

Exclusion criteria

- Pregnant women who suffered from chronic hypertension,
- Proteinuria,
- Epilepsy,
- Kidney disorder or any other serious medical condition.

We took care not to include any study population more than once if it featured in more than one publication.

Step 4: Type of intervention

Methyldopa vs labetalol in PIH.

Step 5: Clinical outcome measure

Primary Outcome:

Significant decrease in mean arterial pressure (MAP) after treatment with methyldopa and labetalol.

Secondary Outcome:

Adverse effects assessment between methyldopa and labetalol.

Step 6: Data extraction

We extracted systolic blood pressure (SBP) and diastolic blood pressure (DBP) or the MAP depending on their availability before and after treatment in individual RCTs of the primigravid pregnant women. MAP = (2DBP + SBP)/3. The prevalence of individual adverse effects of the respective drugs was also extracted. Data were extracted into a data extraction form using standard QUOROM (2000) reporting guidelines. Data were verified by two independent researchers, and any discrepancies were resolved by consensus.

Data were extracted for the prevalence of adverse effects caused by the active drugs from the included RCTs. They were later compared.

Step 7: Nullification of bias

Authors assured to include studies in which allocation of control and experimental groups were adequately randomized and there was no conflict of interest as well as match to inclusion and exclusion criteria.

Step 8: Measures of treatment effect

A direct comparison between methyldopa and labetalol was done using a fixed and random effect model and standardized mean deviation (SMD) was calculated. Data from publications comparing the two antihypertensive monotherapies with each other was used to calculate the difference in the before and after treatment MAP of each drug for the individual RCTs. These differences were taken into account to perform a meta-analysis and generate the SMD for individual RCTs.

Step 9: Summary measures

A fixed and random effect model test was used for a direct comparison between active drugs. The principal summary measure was done with a 95% confidence interval with SMDs and funnel as well as a forest plot. RevMan®Version 5.38 was used for analysis. The I^2 test was used to measure the heterogeneity. A paired *t*-test was performed to find if there was a significant difference in the number of adverse effects between the drugs. A *P* value of less than 0.05 was considered significant.

Results

As shown in Figure 1, a total of 58 published papers were identified and 48 of those were rejected for various reasons. As per Table 1, two were review articles rather than original research, 33 were not randomized clinical trials, and 13 were published as abstracts. The remaining 10 studies including 1,200 primigravid pregnant women suffering from PIH were included in the meta-analysis. These remaining studies compared methyldopa and labetalol on their effect in reducing the blood pressure in these women and their respective adverse effects.

Data for clinical evaluation for comparing the efficacy was available in all the 10 studies. In some studies, the blood pressure was given in the form of systolic blood pressure (SBP) and diastolic blood pressure (DBP) while in some in the form of MAP. To standardize the analysis and make the work more convenient, the only MAP was extracted from all the studies using the formula (2DBP + SBP)/3 = MAP in those required.

610 pregnant women were given labetalol of dose 250–1000 mg/day. Table 2 shows the MAP (mmHg) before and

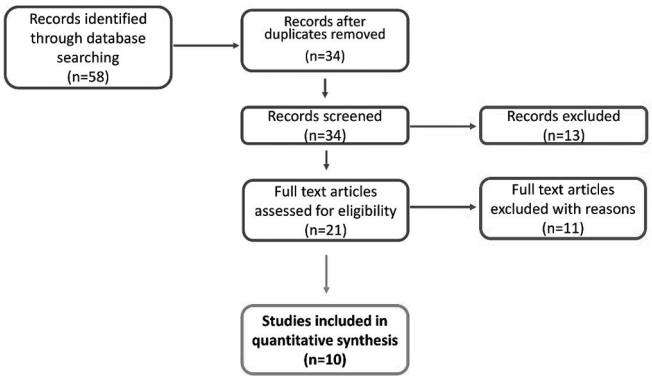

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram

Table 1: Studies included in the meta-analysis

Sr. No	Study ID	Sample size	Methyldopa	Labetalol	Type of study	References
1	Bidisha Roychoudhury (2015)	400	200	200	Drug Comparison, RCT	14
2	Vaidehi Subhedar (2013)	180	90	90	Drug Comparison, RCT	15
3	G.D.Lamming (1979)	19	9	10	Drug Comparison, RCT	16
4	Mary Rohini Pentareddy (2017)	60	30	30	Drug Comparison, RCT	17
5	Nidhi Maheshwari (2016)	60	30	30	Drug Comparison, RCT	18
6	Reena Verma (2012)	90	45	45	Drug Comparison, RCT	19
7	Kavita Babbar (2015)	108	56	52	Drug Comparison, RCT	20
8	Afzal Qasim (2014)	120	60	60	Drug Comparison, RCT	21
9	Archana Bharti (2016)	78	39	39	Drug Comparison, RCT	22
10	Shaba N. Molvi (2012)	85	51	24	Drug Comparison, RCT	23

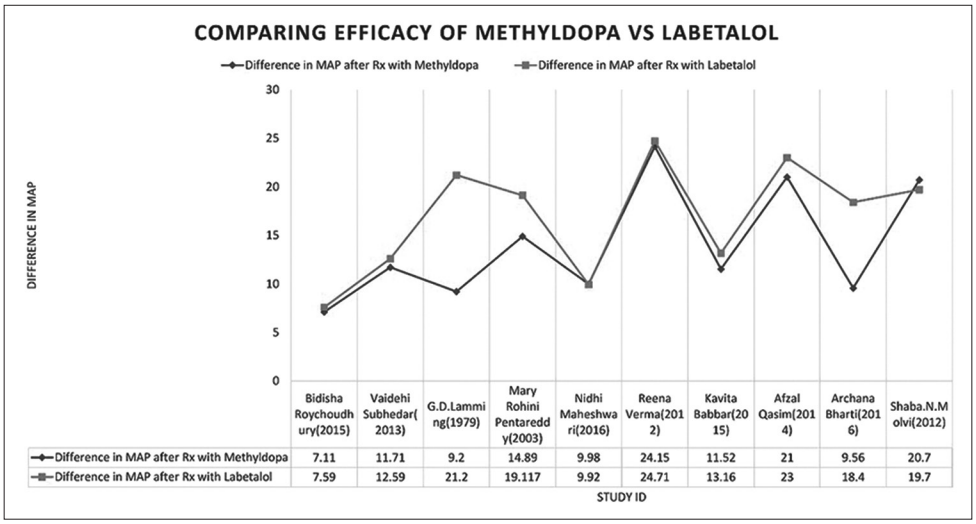

Figure 2: Comparing the efficacy of active drug

Table 2: Effect of labetalol

Sr No. of study	No of cases (nl)	MAP Before RX (mmHg)	MAP After Rx (mmHg)	*P* value
Bidisha Roychoudhury (2015)	200	115.29±4.39	107.7±2.59	<0.001
Vaidehi Subhedar (2013)	90	109.49±2.78	96.9±2.7	<0.05
G.D.Lamming (1979)	10	112.9±4.9	91.7±7.1	<0.001
Mary Rohini Pentareddy (2003)	30	112.337±6.6	93.22±5.23	<0.001
Nidhi Maheshwari (2016)	30	111.28±5.28	101.36±6.932	<0.001
Reena Verma (2012)	45	117.74±8.63	93.03±7.08	<0.05
Kavita Babbar (2015)	52	109.56±4.3	96.4±5.1	<0.05
Afzal Qasim (2014)	60	116.67±8.33	93.67±7.66	<0.05
Archana Bharti (2016)	39	131.47±8.1	113.07±8.067	<0.01
Shaba. N.Molvi (2012)	34	114±4.5	94.33±6	<0.0001
Total	610	115.0737 (Mean)	98.138 (Mean)	<0.001

Table 3: Effect of methyldopa

Sr No. of study	No. of cases(n2)	MAP Before RX (mmHg)	MAP After Rx (mmHg)	*P* value
Bidisha Roychoudhury (2015)	200	120.5±6.37	113.39±3.32	<0.001
Vaidehi Subhedar (2013)	90	109.86±2.91	98.15±3.44	<0.05
G.D.Lamming (1979)	9	110±6.7	100.8±11.9	<0.01
Mary Rohini Pentareddy (2003)	30	110.443±6.06	95.553±4.58	<0.001
Nidhi Maheshwari (2016)	30	109.91±5.68	99.93±9.35	<0.001
Reena Verma (2012)	45	118.51±7.53	94.36±8.04	<0.05
Kavita Babbar(2015)	56	109.72±5.5	98.2±5.3	<0.05
Afzal Qasim (2014)	60	117.33±8.66	96.33±7.33	<0.05
Archana Bharti (2016)	39	132.53±8.367	122.97±11.033	<0.01
Shaba. N.Molvi (2012)	51	115±3	94.3±6	<0.0001
Total	590	115.3803 (Mean)	101.3983 (Mean)	<0.001

after treatment with labetalol (n1) for individual researches. 590 pregnant women were given methyldopa of dose 100–400 mg/day. Table 3 shows the MAP (mmHg) before and after treatment with Methyldopa (n2) for individual researches.

Both of the drugs show a decrease in the MAP (mmHg) after their consumption. Figure 2 compares the efficacy of these drugs. Here, the differences in the MAP before and after the treatment for both the drugs in individual studies are plotted. These differences were taken into account to perform a meta-analysis and SMDs were generated. During the statistical procedure, labetalol was considered n1 while methyldopa n2. A forest plot [Figures 3 and 4] is plotted to display these.

In a majority of the studies ($n = 8$) the difference in the reduction of MAP was higher in labetalol than methyldopa.

Lamming (1979) (SMD is +2.931) and Bharti (2016) (SMD is +2.321)[16] showed the highest difference [Table 4].[22] While in one study Maheshwari (2016) (SMD is −0.02) the drugs were found to be equally efficacious.[18] But, in only one study Shaba. Molvi (2012) (SMD is −0.394) the efficacy of methyldopa was found better than labetalol [Table 4].

Figure 5 shows the prevalence of adverse effects for each drug in eight studies except Maheshwari (2016) and Lamming (1979). Paired and unpaired t-tests were performed to show if there was a significant difference in the number of adverse effects caused between the drugs. Out of the six adverse effects, there was a significant difference found in drowsiness ($P = 0.023$) which was seen more in Methyldopa complemented patients.

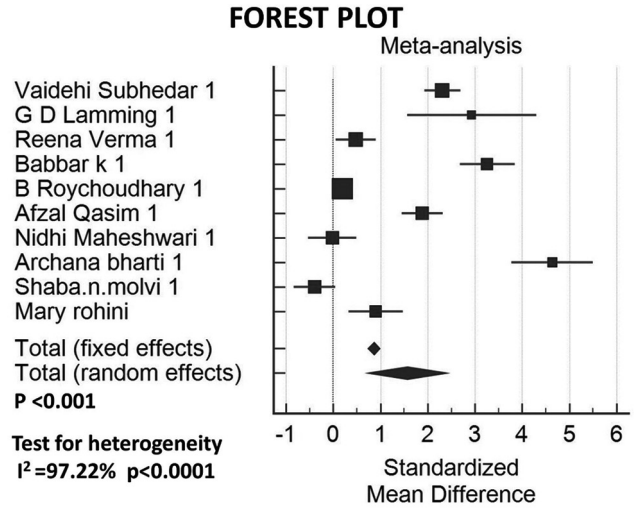

Figure 3: Forest plot

Discussion

The primary objective of management in women with PIH is to protect the safety of the mother and the fetus and the subsequent delivery of a healthy baby. It is crucial to remember that up to a quarter of patients with PIH may progress to preeclampsia, with nearly 10% of the patients progressing to develop eclampsia.[24-26] Furthermore, as was shown in a recent case series of patients with preeclampsia,[27] pregnant women who develop hemorrhagic stroke in the setting of hypertension generally have BP well below the traditional levels of severe hypertension. In this context, the demonstration in the present study that early antihypertensive treatment of PIH reduces both the progression of hypertension and the development of proteinuria is clinically important.

As stated, methyldopa is the oldest drug giving promising results while labetalol is rather a unique drug and its efficacy in treating PIH were still unknown. In the present

Table 4: SMDs with 95% CI

Study	SMD	95% CI
Bidisha Roychoudhury (2015)	0.191	-0.00536 to 0.388
Vaidehi Subhedar (2013)	2.312	1.933 to 2.691
G.D.Lamming (1979)	2.931	1.566 to 4.297
Mary Rohini Pentareddy (2003)	0.898	0.326 to 1.469
Nidhi Maheshwari (2016)	-0.0208	-0.531 to 0.489
Reena Verma (2012)	0.481	0.0597 to 0.903
Kavita Babbar (2015)	3.257	2.676 to 3.837
Afzal Qasim (2014)	1.887	1.454 to 2.320
Archana Bharti (2016)	4.635	3.772 to 5.499
Shaba.N.Molvi (2012)	-0.394	-0.835 to 0.0462
Total (fixed effects)	0.86	0.733 to 0.987
Total (random effects)	1.568	0.735 to 2.401

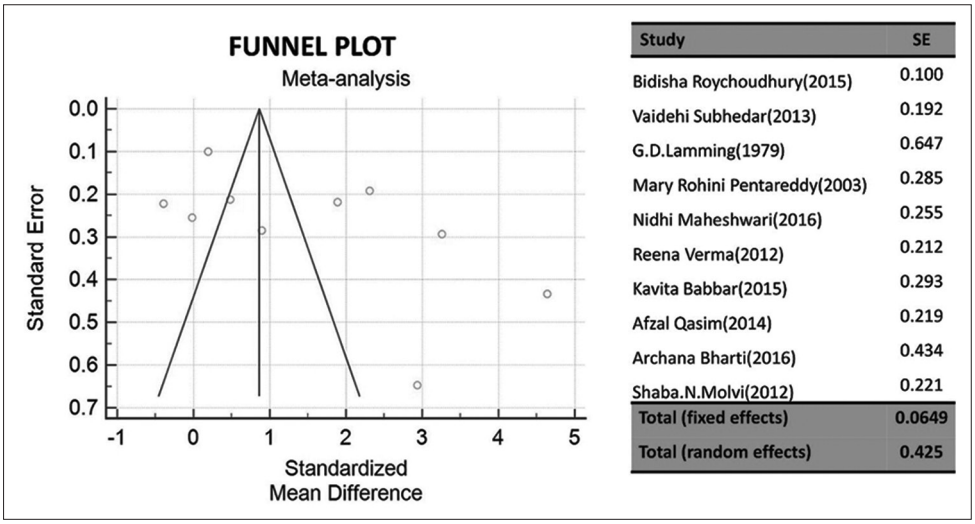

Figure 4: Funnel plot with SE

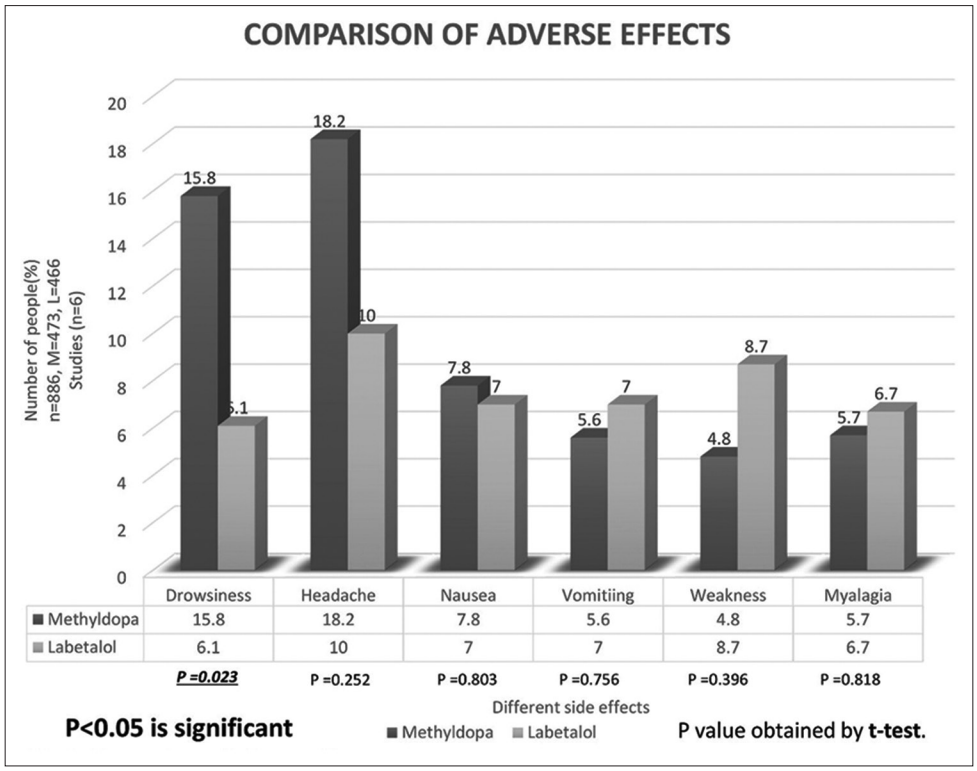

Figure 5: Comparison of adverse effects

study, antihypertensive medication was associated with a significantly reduced incidence of composite maternal endpoint, even after adjustment for other predictors of adverse maternal outcomes. These findings suggest that routine antihypertensive therapy for PIH may offer protection against some non-fatal maternal adverse events. Hence, it can be inferred that the starting of antihypertensives in pregnant women with gestational hypertension produces a significant reduction in blood pressure.

According to this meta-analysis majority of the studies showed labetalol to be efficacious and even quicker than its competitor in treating PIH. Roychoudhary (2015),[14] Subhedar (2015),[15] Lamming (1979),[16] Pentareddy (2013),[17] Verma (2012),[19] Babbar (2015),[20] Qasim (2014),[21] and Bharti (2015)[22] these all studies showed significantly higher ($P < 0.05$) efficacy of labetalol.[20-22] 51% of the primigravids were given labetalol and 49% of the primigravids were given methyldopa.[14-23]

Drowsiness, headache, nausea, vomiting, weakness, and myalgia are the six adverse effects that are caused by both drugs. Of all the side effects, methyldopa regularly causes drowsiness and its tendency to cause it is significantly more than labetalol with $P = 0.023$. There was no significant difference in the prevalence of the other maternal side effects by the drugs as their *P* value after doing paired and unpaired t-test was more than 0.05. Headache ($P = 0.252$), nausea ($P = 0.803$), vomiting ($P = 0.756$), weakness ($P = 0.396$), myalgia ($P = 0.818$). Drowsiness is particularly disturbing to individuals doing mental work and represents the overall most important side effect. Methyldopa being a more central drug may be a cause for it.

Although this analysis has limited studies ($n = 10$), as a majority of the studies show Labetalol to be significantly superior, a robust assessment of publication bias was achievable.

Conclusion

This analysis showed that labetalol is more advantageous than methyldopa in terms of better and quicker control of blood pressure. Labetalol has comparatively fewer maternal side-effects with the good prenatal outcomes. Thus, Labetalol having less maternal side effects is a smarter choice for treating PIH for better outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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