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Full Length Article

Management of hypertension in the early postpartum: A randomized controlled trial

Rossana M.C.P. Marques [a,b,*], Sabina B. Maia [b], André T.V. Araújo [b], Lara M.C. Araújo [b], Thereza V.Q. Dias [b], Gabriela T.B.R. Nogueira [b], Luiz A. Bortolotto [c]

[a] Heart Institute (InCor), Teaching Hospital, School of Medicine, University of São Paulo, São Paulo, SP, Brazil
[b] Lauro Wanderley Teaching Hospital, João Pessoa, Paraíba, Brazil
[c] Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

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ABSTRACT

Objectives: To evaluate blood pressure control during the immediate postpartum period in hypertensive women who had used methyldopa during pregnancy, comparing continuation of that drug with switching it for captopril.
Study design: A single-blind, randomized clinical trial involving 172 postpartum women with hypertension who had previously used methyldopa during pregnancy at a minimum dose of 750 mg/day for at least one week prior to delivery. The subtypes of hypertension included were gestational hypertension, chronic hypertension, pre-eclampsia, superimposed preeclampsia, HELLP syndrome and eclampsia. Following delivery, the patients were randomized either to continue with methyldopa at a minimum dose of 250 mg, three times a day (methyldopa group, n = 88) or to switch to captopril at an initial dose of 25 mg, three times a day (captopril group, n = 84).
Main outcome measures: Logistic regression was used to compare the groups regarding the potential to maintain blood pressure below 140/90 mmHg at over 50 % of measurements postpartum.
Results: In the 48 h following delivery, no significant differences were found between the groups regarding blood pressure control (methyldopa 92.0% versus captopril 95.2%), side effects, postpartum depression (Edinburgh Postnatal Depression Scale) or other clinical outcomes (hypertensive peaks, time to blood pressure control, additional medication use, or maternal and neonatal complications).
Conclusion: Continuation of antihypertensive treatment with methyldopa in the postpartum period yielded similar results to switching it for captopril, both with regard to the efficacy in controlling blood pressure and the safety of the treatment.

1. Introduction

Hypertensive disorders affect around 10 % of all pregnant and postpartum women worldwide and represent an important cause of maternal mortality [1,2]. Hypertensive diseases have been a particularly important cause of death in Latin America and the Caribbean [2]. In Brazil, hypertension remains the principal cause of maternal mortality [3]. The postpartum period is as risky as pregnancy, since almost 50 % of deaths occur postpartum [4], and women can be particularly susceptible to hypertensive disorders in the early postpartum period [5].

Some antihypertensives such as hydralazine, slow-release nifedipine, methyldopa and labetalol are recommended during pregnancy in view of their reduced risk of fetal abnormalities and their proven effectiveness [5–7]. In the postpartum period, although lactation should always be taken into consideration [5], from the point of view of the recently delivered woman, any class of antihypertensive can be used, including the angiotensin-converting enzyme (ACE) inhibitors, which are contra-indicated during pregnancy [6,8], but can be more beneficial in the postpartum period than other antihypertensives insofar as renal protection and improved cardiac function are concerned [9].

In practice, methyldopa is the most commonly used hypertensive drug during pregnancy [5,6], due both to its documented fetal safety and easy access, particularly within the public health sector of developing countries [10]. Nevertheless, although also safe during breast-feeding, it should be avoided in the postpartum period because of the risk of postpartum depression [5]. Therefore, in the early postpartum

Abbreviations: ACE inhibitor, Angiotensin-converting enzyme inhibitor; RCT, Randomized clinical trial.

* Corresponding author at: Rua Dr. Ivanildo Guedes Pessoa 184, Apto. 804, Jardim Oceania, 58037-325 João Pessoa, Paraíba, Brazil.
E-mail address: rossanapaivajp@gmail.com (R.M.C.P. Marques).

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period, it is common clinical practice in Brazil to switch methyldopa for another class of antihypertensive immediately following delivery. This could, however, generate a consequent, albeit rare, rebound effect [11,12]. Furthermore, treatment change could lead to an initial loss of blood pressure control until the full effect of the new drug is achieved, resulting in prolonged hospitalization [13]. In some healthcare services, methyldopa is routinely maintained in the postpartum period, also taking into consideration the possibility of a further pregnancy after this period [7].

Managing hypertension during pregnancy has been widely discussed [5,6,10]; however, few studies have dealt with the postpartum period [14–16]. Consequently, the treatment of hypertension in the postpartum period is generally guided by specialist opinion and guidelines based on studies with a low level of evidence [17].

This study aimed to compare the continued use of methyldopa in the early postpartum period with switching it for another class of antihypertensive to control blood pressure in postpartum women with hypertensive syndromes. The drug used in this study was captopril, an ACE

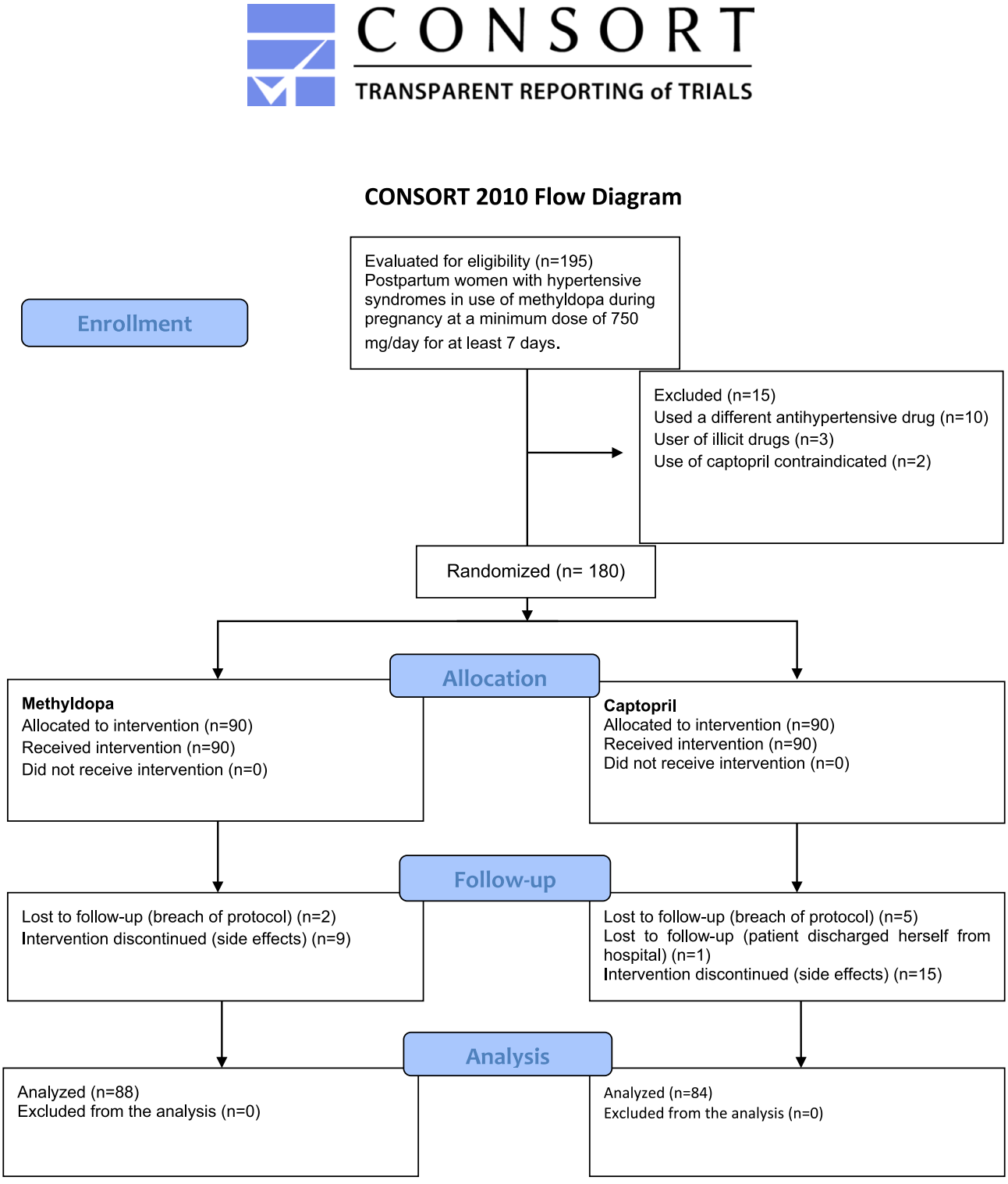

Fig. 1. Procedure for the selection and follow-up of the participants (CONSORT flowchart).

inhibitor with a similar time interval between doses to that of methyldopa (every eight hours), which is widely used in clinical practice and available within the public healthcare sector.

Based on the aforementioned considerations, it is reasonable to conclude that the ideal first-line agent for the treatment of postpartum hypertension remains to be determined. Therefore, more consistent evidence is required to evaluate which antihypertensive agent is the most effective in controlling blood pressure in the postpartum period [17]. The objective of the present study was to evaluate blood pressure control in hypertensive patients in the first 48 h postpartum, comparing those who maintained the use of methyldopa following delivery with patients who switched from methyldopa to another antihypertensive agent, in this case captopril.

2. Materials and methods

This single-blind, drug-controlled, randomized clinical trial (RCT) compared methyldopa with captopril in hypertensive women during the postpartum period.

Data were collected at a teaching hospital, between May 1, 2021 and December 31, 2022. The hospital's internal review board approved the study protocol under reference 15563719.7.0000 and the protocol was registered at Clinical Trials (clinicaltrials.gov) under reference NCT04835233. This study adhered to the CONSORT guidelines and a CONSORT flow diagram is shown in Fig. 1.

The inclusion criteria consisted of all the hypertensive women in the postpartum period who had used methyldopa during pregnancy at a minimum dose of 750 mg/day for a minimum of seven days prior to delivery and who signed the informed consent form. Women in use of any other associated antihypertensive agent, illicit drug users and those with intolerance or contraindication to captopril were excluded from the study.

The hypertensive disorders of pregnancy were defined as chronic hypertension, preeclampsia, superimposed preeclampsia and gestational hypertension [18].

A randomization list was generated using Random Allocation Software, version 2.0, in the proportion of 1 to 1, using the letters A and B for captopril or methyldopa. The drugs were acquired commercially and transferred into identical cartons labeled only as drug A or B by the pharmacist. Allocation concealment and blinding were guaranteed, with neither the investigators nor the statistician being aware of the contents of each box of drugs until the statistical analysis was complete. The patients could identify which drug they were using, since the tablets used were those commercially available, and their shapes and sizes were not identical. Although the nursing staff supervised the administration of the medication, the prescribing physician remained blinded.

Prior to childbirth (T0), laboratory samples were taken, and blood pressure and heart rate were measured. Following delivery (T1), the sealed carton containing the drug and the prescription (1 tablet of A or B every 8 h) was dispensed to the patient in accordance with the randomization list. The initial dose for all the patients was 750 mg/day of methyldopa (one 250 mg tablet every 8 h) or 75 mg/day of captopril (one 25 mg tablet every 8 h).

Blood pressure was measured using a validated automated digital blood pressure monitor (Omron HBP-1100) every four hours during hospitalization following childbirth, except for during the night when the patient was allowed to sleep. All laboratory tests were repeated 24 h after initiation of the study drug.

Controlled blood pressure was defined as systolic pressure (SBP) $<$ 140 mmHg and diastolic pressure (DBP) $<$ 90 mmHg at more than 50 % of measurements within the first 48 h of use of the medication. A blood pressure spike was defined as SBP $\geq$ 160 mmHg and/or DBP $\geq$ 110 mmHg. Discharge criteria included good clinical condition, normal laboratory tests, and no postpartum complications. Upon discharge (T2), the patient received a sufficient supply of the prescribed medication and instructions to monitor blood pressure at home whenever possible. An outpatient visit was scheduled for 15 days after delivery (T3) to measure blood pressure in the clinic and evaluate the home blood pressure measurements in order to determine whether the antihypertensive was still required. At this visit, the Edinburgh Postnatal Depression Scale was also applied (Fig. S1) [19,20].

Treatment during hospitalization followed the registered protocol (Fig. 2). If blood pressure failed to come under control within 48 h of randomization, the dose of either drug was doubled and maintained for another 48 h until further adjustment. If control was not achieved, amlodipine 5 mg, once daily, was added, with the dose being increased to 10 mg/day if necessary. If blood pressure failed to come under control after another 48 h, metoprolol 50 mcg/day was added. In case of a hypertensive peak (SBP $\geq$ 160 mmHg and/or DBP $\geq$ 110 mmHg), clonidine 0.15 mg was instituted orally.

For the sample size calculation, it was assumed that captopril would control blood pressure in approximately 64 % of cases, as previously reported [21]. Furthermore, the study aimed to detect a minimum difference of 20 % in effectiveness between captopril and methyldopa. This was targeted with a power of 80 % (1-$\beta = 0.80$), using a two-proportion comparison test at a significance level (α) of 5 % [22]. A sample size of 150 postpartum women was estimated. To compensate for a potential dropout rate of 20 %, this size was subsequently adjusted to 180 participants, with an equal distribution between the two groups (90 women in each group).

For analysis, R software, version 4.0.5 was used. Significance level was set at $P < 0.05$. Qualitative variables (absolute and relative frequencies) were compared using the chi-square test or Fisher's exact test. Quantitative variables with normal distribution (means $\pm$ SD) were compared using the *t*-test, while the Wilcoxon test was applied to non-normal distributed data (medians and IQR). The Kolmogorov-Smirnov test was used to verify normal distribution.

A logistic regression model [23] with no adjustments for confounders was used to compare the likelihood of blood pressure being found to be under control at 50 % of measurements. SBP, DBP, heart rate and mean blood pressure, as measured every four hours, were compared between groups using a mixed linear model [24].

3. Results

Of the 195 women initially recruited, 10 were excluded because they were using another antihypertensive in association with methyldopa, 3 because of illicit drug use, and 2 due to reported previous side effects with captopril. Therefore, 180 patients were randomized: 90 to the methyldopa group and 90 to the captopril group. During follow-up, 8 patients were excluded from the study due to a breach of protocol. In the methyldopa group, 2 patients had an insufficient number of recorded blood pressure measurements. In the captopril group, 6 patients were excluded, as 1 left the hospital against medical advice; 1 had an insufficient number of recorded blood pressure measurements; and 4 failed to comply with instructions and continued taking methyldopa as prescribed prenatally. In both groups, some patients had to be discontinued from the study due to side effects of the drugs (9 in the methyldopa group and 15 in the captopril group); however, they were not excluded from the analysis. The final analysis included 88 patients in the methyldopa group and 84 in the captopril group (Fig. 1).

In the overall sample, mean age was 30 $\pm$ 7.2 years and 80.8 % were of mixed race, with no differences between the groups. A Cesarean section was performed in 66.3 % of the women, at a mean gestational age of 38.1 weeks (37.1 versus 39.0 weeks, $P = 0.334$). Regarding parity, 38/88 women (43.2 %) and 39/84 (46.4 %) in the methyldopa and captopril groups, respectively, had had $\geq$ 3 pregnancies. Comorbidities were similar in both groups, with 12.2 % of the patients having diabetes, 6.4 % being obese and 4.7 % having both conditions.

Chronic hypertension was prevalent (48.8 %), with no difference in the distribution of the different hypertensive syndromes between the groups. At admission, there was no statistically significant difference

Fig. 2. Protocol for the management of the patients selected for inclusion in the study.

between the groups with respect to mean blood pressure or in the laboratory tests (Table 1).

The groups were also similar regarding mean SBP, DBP, blood pressure and heart rate during hospitalization (Table 2) and, after the intervention, the control of blood pressure within the 48 h after delivery was similar in the two groups (Table 3). At admission, 12/172 patients had blood pressure spikes, 6 patients in each group. The mean number of blood pressure spikes following the intervention was similar between the groups.

There were no inter-group differences with respect to the need to double the dose of antihypertensive or to add other drugs, the number of associated drugs, the need to discontinue or reduce the drug, or in the use of an antihypertensive at discharge from hospital (Table 3).

There were no statistically significant differences in the frequency of side effects between the groups. The scores for the Edinburgh Postnatal Depression Scale also showed no significant differences, with a median of 4.0 (IQR: 0.0–9.8) for the methyldopa group versus 4.0 (1.0–9.0), for the captopril group; $P = 0.699$ (Table 3). Only three patients had SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg 15 days after delivery (outpatient visit), with no significant differences between the groups.

4. Discussion

Maintaining methyldopa in the postpartum period or switching it for captopril yielded a similar response in the control of blood pressure in the first 48 h following childbirth in hypertensive women. In the absence of specific guidelines, obstetric units have either maintained the use of methyldopa in the postpartum period or switched it for another antihypertensive. To the best of our knowledge, this is the first RCT to compare maintaining methyldopa in the early postpartum period with switching it for another antihypertensive, in this case captopril.

Few studies on the control of hypertension in the postpartum period

Table 1
Baseline characteristics at admission of the 172 hypertensive patients according to their allocated group.

Characteristics	Total (n = 172)	Methyldopa (n = 88)	Captopril (n = 84)	*P*-value *
Age, years; mean ± SD	30.2 ± 7.2	30.0 ± 7.2	30.4 ± 7.3	0.692
Gestational age; mean	38.1	38.1	38.1	0.667
Number of pregnancies; n (%)				
1	58/172 (33.7)	30/88 (34.1)	28/84 (33.3)	0.890
2	37/172 (21.5)	20/88 (22.7)	17/84 (20.2)	
≥ 3	77/172 (44.8)	38/88 (43.2)	39/84 (46.4)	
Parity; n (%)				
1	64/170 (37.6)	32/87 (36.8)	32/83 (38.6)	0.928
2	40/170 (23.5)	20/87 (23.0)	20/83 (24.1)	
≥ 3	66/170 (38.8)	35/87 (40.2)	31/83 (37.8)	
Mode of delivery; n (%)				
Normal	58/172 (33.7)	33/88 (37.5)	25/84 (29.8)	0.334
Type of hypertensive disorder; n (%)				
Preeclampsia	22/171 (12.9)	9/88 (10.2)	13/83 (15.7)	0.362
Superimposed preeclampsia	12/172 (7.0)	5/88 (5.7)	7/84 (8.3)	0.560
Gestational hypertension	53/172 (30.8)	32/88 (36.4)	21/84 (25.0)	0.137
Eclampsia	0/172 (0.0)	0/88 (0.0)	0/84 (0.0)	–
Chronic hypertension	84/172 (48.8)	41/88 (46.6)	43/84 (51.2)	0.674
HELLP syndrome	1/172 (0.6)	0/88 (0.0)	1/84 (1.2)	0.488
Systolic pressure, mmHg; mean ± SD	128 ± 13.6	125.6 ± 14.0	131.1 ± 12.7	0.070
Diastolic pressure, mmHg; mean ± SD	80.9 ± 12.3	79.7 ± 12.5	82.1 ± 12.0	0.207
Mean blood pressure, mmHg; mean ± SD	96.7 ± 11.9	95.1 ± 12.6	98.4 ± 11.0	0.065
Altered laboratory parameters; n (%)				
Platelets (<100,000 per microliter)	1/172 (0.6)	0/88 (0.0)	1/84 (1.2)	0.488
LDH (>600 U/L)	7/172 (4.1)	2/88 (2.3)	5/84 (6.0)	1.000
AST or ALT (>70 U/L)	6/172 (3.5)	3/88 (3.4)	3/84 (3.6)	1.000
Protein/Creatinine ratio (>0.3)	22/171 (12.9)	11/88 (12.5)	11/83 (13.3)	1.000
Total bilirubin (>1.2 mg/dL)	3/172 (1.7)	1/88 (1.1)	2/84 (2.4)	0.614
Creatinine (≥1.2 mg/dL)	1/96 (1.0)	1/59 (1.7)	0/37 (0.0)	1.000

SD: standard deviation, IQR: interquartile range, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase; * Student's *t*-test, Wilcoxon test, Fisher's exact test or chi-square test.

Table 2
Mean blood pressure and heart rate per day of hospitalization for the 172 hypertensive patients according to their allocated group.

Characteristics	Methyldopa	Captopril	*P*-value *
1st day of hospitalization	n = 79	n = 76	
Systolic pressure, mmHg; mean ± SD	119.5 ± 12.3	119.4 ± 14.0	0.944
Diastolic pressure, mmHg; mean ± SD	71.3 ± 11.7	70.9 ± 10.5	0.830
Mean blood pressure, mmHg; mean ± SD	87.4 ± 10.8	87.0 ± 10.9	0.834
Heart rate, bpm; mean ± SD	83.0 ± 12.7	85.4 ± 14.8	0.286
2nd day of hospitalization	n = 88	n = 84	
Systolic pressure, mmHg; mean ± SD	122.2 ± 12.4	124.4 ± 12.9	0.259
Diastolic pressure, mmHg; mean ± SD	73.5 ± 11.4	75.9 ± 9.0	0.119
Mean blood pressure, mmHg; mean ± SD	89.7 ± 10.6	92.1 ± 9.4	0.123
Heart rate, bpm; mean ± SD	85.7 ± 13.1	84.6 ± 14.7	0.595

n: sample size; SD: standard deviation; mmHg: millimeters of mercury; bpm: beats per minute, * Student's *t*-test.

have been conducted to date [13]. The latest 2021 Brazilian guidelines on hypertension recommend methyldopa as the first drug of choice for treating hypertension during pregnancy [7]. International guidelines, including those of the ACOG, ISSHP, ESC and AHA, emphasize the need to conduct appropriate postpartum screening, control blood pressure and monitor cardiovascular risk factors. In general, all classes of antihypertensives could be used, including beta-blockers and diuretics in certain selected cases. Nevertheless, the recommendations in the different guidelines remain vague and imprecise [25].

Postpartum hypertension may be related to a combination of factors, including the intravenous administration of a large volume of fluids to patients undergoing Cesarean section [26]. In this study, the majority of patients were delivered by Cesarean section and no differences in blood pressure control were found between the groups.

Rebound hypertension may occur following discontinuation of almost all types of antihypertensive but, principally, with those such as clonidine, beta-blockers and methyldopa that reduce sympathetic activity [27]. Abrupt cessation can lead to sympathetic overactivity, generating symptoms such as nervousness, tachycardia, headache, agitation, nausea and, less commonly, a rapid increase in blood pressure to pretreatment levels or higher and/or myocardial ischemia [27]. No sudden increase in blood pressure was found when methyldopa was abruptly stopped and switched for captopril. In fact, the rate of blood pressure control (SBP < 140 mmHg and DBP < 90 mmHg in the 48 h following childbirth) was excellent (>90 %) irrespective of the drug used.

Due to its mechanism of action in the brainstem, methyldopa is not recommended during the postpartum period as it can provoke undesirable side effects including decreased mental alertness, possibly affecting the woman's ability to care for her newborn infant [5]. In this study, there were no reports of increased drowsiness in the methyldopa group.

The use of methyldopa in the postpartum period can also increase the likelihood of postpartum blues and depression [28]. Postpartum blues affect around 43 % of women on the third day after childbirth, while postpartum depression affects 10–15 % of women [29]. Pregnancy-induced hypertension and postpartum mood disorders may be interconnected, and the link between them could be methyldopa [30]. A study showed that 77.8 % of the women who scored highly in the Edinburgh Postnatal Depression Scale were in use of methyldopa [30]. Conversely, in the present study, the depression scores were similar in both groups, showing no increased risk to the patients who continued with methyldopa in the postpartum period. Nevertheless, the analysis was performed only once, 15 days following delivery. Furthermore, establishing the association between depression and the use of any specific drug is difficult because the patient is exposed to various stressors typical of the postpartum period such as sleep deprivation, hormone fluctuations and the demands of having to care for a newborn infant.

The current results suggest that maintaining the use of methyldopa in hypertensive women who had been using this drug prior to childbirth may constitute a safe and effective alternative for blood pressure control in the first 48 h following delivery.

Comparison with other studies is impossible, since there are no systematic reviews or clinical trials that compared the continued use of methyldopa following childbirth with switching to another antihypertensive. Because this is a heterogenous population, further studies with

Table 3
Clinical parameters and comparison of the rate of blood pressure control in the 48 h after initiating use of methyldopa or captopril for the treatment of hypertension in postpartum women with pregnancy-related hypertensive disorders.

Characteristics	Methyldopa (n = 88)	Captopril (n = 84)	*P*-value	
Need to double the initial dose of the drug used to control blood pressure; n (%)	4/88 (4.5)	3/84 (3.6)	1.000 *	
Need to associate another drug to control blood pressure; n (%)	2/88 (2.3)	3/84 (3.6)	0.677*	
Number of associated drugs required to control blood pressure; median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.610**	
Need to suspend the dose; n (%)	15/88 (17.0)	11/84 (13.1)	0.527 *	
Need to reduce the dose; n (%)	2/88 (2.3)	0/84 (0.0)	0.496 *	
Use of antihypertensive at discharge from hospital; n (%)	72/88 (81.8)	69/84 (82.1)	1.000*	
Side effects [a]				
Dizziness; n (%)	13/88 (14.8)	15/84 (17.9)	0.681*	
Orthostatic hypotension; n (%)	10/88 (11.4)	11/84 (13.1)	0.818*	
Headache; n (%)	7/88 (8.0)	8/84 (9.5)	0.791*	
Nausea; n (%)	6/88 (6.8)	8/84 (9.5)	0.585*	
Dry mouth; n (%)	7/88 (8.0)	4/84 (4.8)	0.536*	
Decreased mental alertness /drowsiness; n (%)	3/88 (3.4)	6/84 (7.1)	0.321*	
Dry cough; n (%)	1/88 (1.1)	6/84 (7.1)	0.060*	
Postpartum depression; median (IQR) [b]	4.0 (0.0–9.8)	4.0 (1.0–9.0)	0.699**	
Control of blood pressure; n (%) [c]	**Methyldopa (n = 88)**	**Captopril (n = 84)**	**Odds Ratio (95 % CI)**	***P*-value**
	81/88 (92.0)	80/84 (95.2)	0.58 (0.15; 1.99)	0.397***

n: sample size; % percentage; CI: confidence interval; [a] 24 hours after the intervention and while the patient was in hospital; [b] Edinburgh Postnatal Depression scale; [c] Systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg at > 50 % of measurements in 48 h; * Fisher's exact test; ** Wilcoxon test; *** Logistic regression model (McCullagh and Nelder).

selected samples are crucial.

Although this is a well-designed RCT, the current sample size is small, particularly for the purpose of evaluating the rebound effect or withdrawal syndrome, which is a rare event, and to assess methyldopa-associated depression. Another limitation refers to the inclusion of patients with any form of hypertensive syndrome, i.e. gestational hypertension, chronic hypertension, preeclampsia and superimposed preeclampsia. Consequently, it is unknown whether the outcomes would have been different for specific subgroups, since the physiopathology differs.

Additionally, the primary outcome was found in a high frequency of participants in both groups (over 90 %), exceeding the estimated effect used in the calculation of sample size. This may have reduced the study's ability to detect subtle differences and could potentially result in a type II error. To address this, future studies could recalibrate expected effects based on updated data and may consider increasing sample size to improve statistical power. Furthermore, exploring alternative outcomes could provide deeper insights that could have been obscured due to the high occurrence rate of the primary outcome.

In the majority of the patients included here, increases in blood pressure were moderate to low, with severe cases being rare. This probably occurred because patients who were in use of associated antihypertensives were excluded from the study, since this study question was whether to maintain methyldopa or switch it for another class of antihypertensive. Otherwise, if we had not excluded those patients, the results could have been compromised due to a possible interaction between the drugs through different mechanisms of action. Therefore, the predominant population here, with a mild to moderate increase in blood pressure, could constitute a limitation to the extrapolation of these results to the population with higher blood pressure levels or who are in use of associated antihypertensive agents.

Finally, the data were analyzed 48 h after delivery, while the patients were still hospitalized. Longer-term assessments, such as those at six weeks postpartum, were not possible due to the challenges of monitoring patients at home.

5. Conclusions

Maintaining methyldopa in the postpartum period or switching it for another class of antihypertensive (captopril) proved equally effective in controlling blood pressure in the first 48 h following childbirth for hypertensive women who had previously been in use of methyldopa. Consequently, antihypertensive treatment with methyldopa in the first 48 h postpartum may constitute a safe and effective alternative for blood pressure control during this period, allowing a later scheduled switch to an antihypertensive with simpler posology and fewer side effects. Nevertheless, when defining their protocol, each healthcare center should take the characteristics of the population into consideration as well as the frequency of episodes of hypertension in postpartum women and the confidence and experience of the medical team in using the drug. Further studies should assess blood pressure control, rebound effects, and include larger, well-defined populations with specific hypertensive disorders in pregnancy. Evaluating the first weeks postpartum could help develop evidence-based clinical protocols.

Research Data: https://docs.google.com/spreadsheets/d/1NVKMkncaA9ccxEK1xV4TWqNUK4178Pgb/edit?usp=sharing&ouid=115291512040655229716&rtpof=true&sd=true.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2025.101195.

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