Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 27 (2022) 173–175

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Short communication

Differential effects of renin-angiotensine-aldosteron system inhibition, sympathoinhibition and low sodium diet on blood pressure in women with a history of preeclampsia: A double-blind, placebo-controlled cross-over trial (the PALM study)

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ARTICLE INFO

Keywords:
Preeclampsia
Postpartum
Hypertension
Renin-angiotensin-aldosterone system inhibition
Sympathoinhibition
Low sodium diet
Cross-over trial

ABSTRACT

Current guidelines lack sufficient evidence to recommend a specific blood pressure lowering strategy to prevent cardiovascular disease after preeclampsia. We conducted a double-blind cross-over trial to identify the most potent antihypertensive strategy: renin-angiotensin-aldosterone system (RAAS) inhibition (losartan), sympathoinhibition (moxonidine), low sodium diet and placebo (n = 10). Due to low inclusion rate our study stopped prematurely. Initiatory analyses showed no significant effect of antihypertensive strategy on office blood pressure and 24-hour blood pressure. However, nocturnal dipping was significantly higher on RAAS inhibition and low sodium diet compared to placebo and sympathoinhibition.

Optimal cardiovascular prevention after preeclampsia should be further explored.

1. Introduction

Preeclampsia affects 2–5% of all pregnancies and is characterized by de novo hypertension and proteinuria or maternal organ dysfunction or uteroplacental dysfunction resulting in fetal growth restriction [1–3]. Women with a history of preeclampsia have an increased risk to develop hypertension and cardiovascular events [2,4–7].

Current guidelines for prevention of cardiovascular disease after preeclampsia lack sufficient evidence to recommend a particular blood pressure lowering strategy [8–11]. In a recent systematic review, no particular treatment or approach regarding cardiovascular risk management after hypertensive pregnancy disorders could be identified [12].

The aim of this cross-over trial was to investigate the most effective blood pressure lowering strategy in women with a history of preeclampsia with (borderline) hypertension.

2. Methods

Based on Dorresteijn et al., we performed a randomized, double-blind, four-way crossover trial in women aged 18–45 years with a history of early-onset preeclampsia who were at least 6 months postpartum and had off-treatment diastolic blood pressure > 80 mmHg and/or systolic blood pressure > 120 mmHg assessed by office readings at two visits (PALM-study, NTR4590) [13].

Exclusion criteria were diastolic blood pressure > 110 mmHg and/or systolic blood pressure > 180 mmHg, use of more than one antihypertensive drug, current pregnancy, smoking, any other medical condition or use of other medication.

In each woman the effects of 8 weeks inhibition of renin-angiotensin aldosterone system (RAAS) inhibition (losartan 100 mg), sympathoinhibition (moxonidine 0.4 mg), low sodium diet (50 mmol NaCl/24 h) and placebo on office blood pressure and 24-hour blood pressure

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https://doi.org/10.1016/j.preghy.2021.12.016
Received 14 May 2020; Accepted 31 December 2021
Available online 6 January 2022

Table 1
Baseline characteristics.

Characteristics (n = 8)		No (%) or median (IQR)
Age (years)		39 (29–43)
BMI (kg/m2)		24 (23–25)
Waist circumference (cm)		83 (75–100)
Hip circumference (cm)		99 (84–102)
Blood pressure (mmHg) at screening	Systolic	138 (135–145)
	Diastolic	89 (80–98)
Antihypertensive use	Yes	2 (25%)
	No	6 (75%)
Smoked	Current	0 (0%)
	Never	6 (75%)
	Quit	2 (25%)
Time since last PE (years)		6 (1–12)
Pregnancies complicated with PE	1	7 (88%)
	2	1 (13%)
Gestational age of PE pregnancy (weeks)		30 (29–35)
Birth weight of PE pregnancy (gram)		1080 (998–2002)

(mean arterial blood pressure (MAP)) were determined. Nocturnal dipping (%) was assessed, as non-dipping is associated with increased cardiovascular risk [14]. The total study period comprised 32 weeks. Compliance for low sodium was triple-checked in the low sodium diet period using 24-hour urine and compliance for the other periods was performed by counting pills.

For sufficient power to detect 4 mmHg difference we required 30 participants. However, due to intensity and duration of the study the required sample size was not feasible, and at 10 inclusions the study stopped prematurely. The initial study design included additional vascular measurements (stiffness, endothelial function) which were left out during the course of the study, due to the intensity experienced by the participants.

Despite small sample size, we performed statistical analysis on our data to obtain an overview of the results. The data were analyzed using linear mixed models with subject*visit as random factor. P-values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS 21.0.

3. Results

Out of 136 eligible women, 10 women could be randomized and analyses were performed on 8 participants. Main reasons to decline participation included current child wish, expected high intensity of the study and total study duration. Two randomized participations could not be taken into the analyses due to loss of follow-up during the study period.

Median age of the participants was 39 years and their median blood pressure at screening was 138/89 mmHg. All women had early and/or severe preeclampsia, as reflected in the median gestational age at delivery (30 weeks; Table 1).

No significant effect of blood pressure lowering strategy was observed on either office blood pressure and 24-hour blood pressure, although in the 24-hour measurements a trend towards lower MAP was observed on losartan (92 ± 7 mmHg) and low sodium diet (94 ± 14 mmHg) compared to placebo (97 ± 13 mmHg) and moxonidine (98 ± 13 mmHg) (Table 2). Nocturnal dipping of MAP did significantly differ ($p_{strategy} = 0.03$), with increased dipping on low sodium diet (-18 ± 9 mmHg, $p = 0.01$) and losartan (-18 ± 5 mmHg, $p < 0.01$), compared to placebo (-13 ± 3 mmHg) and moxonidine (-6 ± 6 mmHg). Compliance was lowest on moxonidine (mean number of pills returned: 23 (19–93). Urinary sodium was clearly lower in the low sodium period compared to the other study periods, especially at weeks 2 and 4.

4. Discussion

This double-blind cross-over trial is unique in aiming to find a specific cardiovascular treatment strategy in women after preeclampsia. Since inclusion of participants and adherence to study interventions were extremely difficult, our study provides valuable data despite being stopped prematurely. Although we observed no significant effect of blood pressure lowering strategy on 24-hour blood pressure, there was a trend towards lower MAP on losartan and low sodium diet. In addition, nocturnal dipping was significantly higher on RAAS inhibition and low sodium diet compared to placebo and sympathoinhibition.

Whilst the observed effects are small, these findings fit with the previously reported increased salt-sensitivity and disturbances in RAAS after preeclampsia. Targeting these pathways might provide an effective strategy to prevent cardiovascular disease after preeclampsia [15–17]. In general, female blood pressure is reported to be more sodium sensitive and increased sensitivity of angiotensin II type two receptor therapy has been reported [18,19].

The design of this study was used successfully before in obese diabetic patients and is strong in cross-over design, reducing the influence of confounding covariates since participants serve as their own control [13]. However, our study appeared to be challenging due to its intensity and duration. This might also indicate poor willingness of women with a history of preeclampsia to adjust lifestyle or use medication to prevent development of cardiovascular disease. Regarding lifestyle interventions, our study showed that continuing compliance to low sodium diet is difficult to establish. Due to the low inclusion rate, we were limited in our analyses and had no opportunity to analyze the order of randomization and our intended secondary outcomes, such as arterial stiffness and endothelial function. For both future studies and clinical follow-up of women after preeclampsia we recommend practical treatment strategies, which are better adapted to the lifestyle of these women, and include new techniques like telemonitoring, to ease participation and support compliance.

Table 2
Primary endpoint.

Blood pressure		Placebo (n = 8)	Losartan (n = 8)	Moxonidine (n = 7)	Low sodium diet (n = 7)	P $_{strategy}$
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
24 h mean	Systolic	125 (116–140)	122 (113–125)	124 (115–142)	122 (112–130)	0.86
(mmHg)	Diastolic	80 (71–97)	76 (71–82)	82 (74–98)	75 (68–83)	0.82
	MAP	93 (88–111)	91 (87–96)	96 (92–113)	91 (85–99)	0.82
Nocturnal dip (%)	Systolic	9% (7–11)*	15% (8–19)	6% (0–7)*	14% (11–19)	**<0.001**
(mmHg)	Diastolic	15% (12–17)	21% (11–30)	8% (5–17)	21% (16–25)	0.05
	MAP	13% (11–14)	17% (10–25)	6% (3–11)*	18% (13–22)	**<0.03**
Office	Systolic	121 (113–137)	116 (112–120)	121 (109–125)	115 (110–128)	0.81
(mmHg)	Diastolic	80 (69–91)	71 (67–76)	78 (67–87)	73 (65–86)	0.91
	MAP	88 (85–106)	85 (82–89)	92 (81–100)	86 (80–100)	0.92
24 h Sodium intake	Week 2	–	–	–	47 (33–136)	
(mmol/24 h)	Week 4	–	–	–	57 (50–71)	
	Week 8	115 (76–152)	123 (58–145)	103 (101–188)	90 (77–93)	0.48

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5. Conclusion

Equal beneficial effects of RAAS inhibition and low sodium diet were observed on 24-hour blood pressure, especially on nocturnal dipping, in women with a history of preeclampsia. These findings are in line with previously reported increased salt-sensitivity and disturbances in RAAS after preeclampsia and suggest further exploration which strategy should be recommended to lower blood pressure.

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.

References

[1] S. Hernández-Díaz, S. Toh, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ. 2009;338(January): b2255.
[2] M.C. Brown, K.E. Best, M.S. Pearce, J. Waugh, S.C. Robson, R. Bell, Cardiovascular disease risk in women with pre-eclampsia: Systematic review and meta-analysis, Eur. J. Epidemiol. 28 (1) (2013) 1–19.
[3] B.W.J. Mol, C.T. Roberts, S. Thangaratinam, L.A. Magee, C.J.M. de Groot, G. J. Hofmeyr, Pre-eclampsia, Pre-eclampsia. Lancet. 387 (10022) (2016) 999–1011.
[4] L. Bellamy, J.-P. Casas, A.D. Hingorani, D.J. Williams, Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis, BMJ. 335 (7627) (2007) 974, https://doi.org/10.1136/bmj.39335.385301.BE.
[5] S.D. McDonald, A. Malinowski, Q.i. Zhou, S. Yusuf, P.J. Devereaux, Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses, Am. Heart J. 156 (5) (2008) 918–930.
[6] T.K.J. Groenhof, G.A. Zoet, A. Franx, R.T. Gansevoort, M.L. Bots, H. Groen, A. T. Lely, Trajectory of cardiovascular risk factors after hypertensive disorders of pregnancy, Hypertension. 73 (1) (2019) 171–178.
[7] J.H.W. Veerbeek, W. Hermes, A.Y. Breimer, B.B. van Rijn, S.V. Koenen, B.W. Mol, A. Franx, C.J.M. de Groot, M.P.H. Koster, Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension, Hypertension. 65 (3) (2015) 600–606.
[8] K.Y. Heida, M.L. Bots, C.JM. de Groot, F.M. van Dunné, N.M. Hammoud, A. Hoek, J.SE. Laven, A.H. Maas, J.E. Roeters van Lennep, B.K. Velthuis, A. Franx, Cardiovascular risk management after reproductive and pregnancy related disorders: A dutch multidisciplinary evidence-based guideline, Eur. J. Prev. Cardiol. 23 (17) (2016) 1863–1879.
[9] C. Bushnell, L.D. McCullough, I.A. Awad, M.V. Chireau, W.N. Fedder, K.L. Furie, V. J. Howard, J.H. Lichtman, L.D. Lisabeth, I.L. Piña, M.J. Reeves, K.M. Rexrode, G. Saposnik, V. Singh, A. Towfighi, V. Vaccarino, M.R. Walters, Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the American heart association/American stroke association, Stroke. 45 (5) (2014) 1545–1588.
[10] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, M.-T. Cooney, U. Corrà, B. Cosyns, C. Deaton, I. Graham, M.S. Hall, F.D.R. Hobbs, M.-L. Løchen, H. Löllgen, P. Marques-Vidal, J. Perk, E. Prescott, J. Redon, D.J. Richter, N. Sattar, Y. Smulders, M. Tiberi, H.B. van der Worp, I. van Dis, W.M. M. Verschuren, 2016 European Guidelines on cardiovascular disease prevention in clinical practice, Eur. Heart. J. 37 (29) (2016) 2315–2381.
[11] L. Mosca, E.J. Benjamin, K. Berra, J.L. Bezanson, R.J. Dolor, D.M. Lloyd-Jones, L. K. Newby, I.L. Piña, V.L. Roger, L.J. Shaw, D. Zhao, T.M. Beckie, C. Bushnell, J. D'Armiento, P.M. Kris-Etherton, J. Fang, T.G. Ganiats, A.S. Gomes, C.R. Gracia, C.K. Haan, E.A. Jackson, D.R. Judelson, E. Kelepouris, C.J. Lavie, A. Moore, N. A. Nussmeier, E. Ofili, S. Oparil, P. Ouyang, V.W. Pinn, K. Sherif, S.C. Smith, G. Sopko, N. Chandra-Strobos, E.M. Urbina, V. Vaccarino, N.K. Wenger, Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update: A Guideline from the American Heart Association, Circulation. 123 (11) (2011) 1243–1262.
[12] A.E. Cairns, L. Pealing, J.M.N. Duffy, N. Roberts, K.L. Tucker, P. Leeson, L. H. MacKillop, R.J. McManus, Postpartum management of hypertensive disorders of pregnancy: A systematic review, BMJ Open. 7 (11) (2017) e018696.
[13] J.A.N. Dorresteijn, I.M. Schrover, F.L.J. Visseren, P.G. Scheffer, P.L. Oey, A.H. (. Danser, W. Spiering, Differential effects of renin-angiotensin-aldosterone system inhibition, sympathoinhibition and diuretic therapy on endothelial function and blood pressure in obesity-related hypertension: A double-blind, placebo-controlled cross-over trial, J. Hypertens. 31 (2) (2013) 393–403.
[14] G.F. Salles, G. Reboldi, R.H. Fagard, C.R.L. Cardoso, S.D. Pierdomenico, P. Verdecchia, K. Eguchi, K. Kario, S. Hoshide, J. Polonia, A. de la Sierra, R. C. Hermida, E. Dolan, E. O'Brien, G.C. Roush, Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: The ambulatory blood pressure collaboration in patients with hypertension (ABC-H) meta-analysis, Hypertension. 67 (4) (2016) 693–700.
[15] G. Martillotti, A. Ditisheim, M. Burnier, G. Wagner, M. Boulvain, O. Irion, A. Pechère-Bertschi, Increased salt sensitivity of ambulatory blood pressure in women with a history of severe preeclampsia, Hypertension. 62 (4) (2013) 802–808.
[16] A.R. Saxena, S.A. Karumanchi, N.J. Brown, C.M. Royle, T.F. McElrath, E.W. Seely, Increased sensitivity to angiotensin II is present postpartum in women with a history of hypertensive pregnancy, Hypertension. 55 (5) (2010) 1239–1245.
[17] A.E. Stanhewicz, S. Jandu, L. Santhanam, L.M. Alexander, Increased Angiotensin II Sensitivity Contributes to Microvascular Dysfunction in Women Who Have Had Preeclampsia, Hypertension. 70 (2) (2017) 382–389.
[18] J. Leete, A.T. Layton, Sex-specific Long-term Blood Pressure Regulation: Modeling and Analysis, Comput. Biol. Med. 104 (2019) 139–148.
[19] S. Murao, Y. Takata, M. Yasuda, H. Osawa, F. Kohi, The influence of sodium and potassium intake and insulin resistance on blood pressure in normotensive individuals is more evident in women, Am. J. Hypertens. 31 (8) (2018) 876–885.