

Postpartum arterial hypertension management in patients with severe preeclampsia The experience of a high specialty hospital of Mexico City

ABSTRACT

Background: the management of postpartum hypertension is a priority in severe preeclampsia (SP) to reduce short and long term complications. This study aimed to analyze the results of the management of postpartum arterial hypertension in patients with SP of a high specialty hospital of Mexico City.

Methods: An observational, longitudinal, retrospective and analytical study was carried out in a series of 91 pregnant women with SP admitted to the Intensive Care Unit (ICU) from May 1 to September 30, 2019 with termination of pregnancy and postpartum stay in the same hospital. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and antihypertensive management were compared on admission (prepartum, baseline measurement) and on days 1, 3 and 7 postpartum. Statistical analysis: descriptive statistics, Student t test and two-way ANOVA test with the statistical program SPSS version 20.

Results: age 30.91 ± 6.69 years, parity 2 and pregnancy of 32.48 ± 4.21 weeks. SBP gradually decreased, at the end of the study the changes had statistical significance (baseline measurement 163.08 ± 16.52 , vs day 1 133.78 ± 22.11 $P = .150$, vs day 3 131.56 ± 21.07 $P = 0.051$, vs day 7 125.02 ± 17.79 $P = 0.007$). DBP also decreased, but at the end of the study the changes were not significant (baseline measurement 100.29 ± 13.06 , vs day 1 82.02 ± 13.88 $P = .61$, vs day 3 80.87 ± 11.98 $P = .11$, day 7 78.02 ± 10.78 $P = .14$). At the beginning, the combination of two to five oral drugs was necessary, but in the end the number of drugs was reduced. Blood pressure was controlled ($<140/90$ mmHg) in 87.92% ($n=80$), and 12.08% ($n=11$) continued with uncontrolled hypertension ($\geq 140/90$ mmHg). Stay in the ICU was 2.33 ± 2.12 days, stay in hospital 7.23 ± 3.69 days and mortality 0%.

Conclusion: SBP was significantly improved, but not DBP. Polypharmacy was necessary in most cases. A significant number of patients did not have good blood pressure control.

1. INTRODUCTION

Although removal of the fetus and placenta is considered the definitive treatment for preeclampsia, unusually blood pressure can remain elevated after delivery and last for a

short or permanent period [1]. The incidence of arterial hypertension (defined as blood pressure $\geq 140/90$ mmHg) after 12 weeks postpartum in patients with preeclampsia has been reported to be 27.8% [2]. Its pathophysiology is complex. An intravascular volume overload secondary to the mobilization of water and sodium from the interstitium and the inability of their renal elimination has been implicated. In addition, the decrease of colloid osmotic pressure of plasma proteins and the participation of atrial natriuretic peptide, brain natriuretic peptide, angiotensin I, angiotensin II, aldosterone, vasopressin and adiponectin among other compounds have been implicated [3,4].

Short-term complications include eclampsia, ischemic or hemorrhagic stroke, persistent cerebral edema, posterior reversible leukoencephalopathy, acute pulmonary edema, cardiac dysrhythmia, myocardial ischemia, HELLP syndrome, hepatic subcapsular hematoma, acute kidney injury, renal cortical necrosis bilateral, disseminated intravascular coagulation and the tendency to hemorrhagic uncontrolled with greater frequency of surgical reinterventions [4,5]. Although the risk of acute complications is increased, on the other hand, the access door to chronicity remains open. Patients with postpartum hypertension have a higher frequency of presenting future acute myocardial infarction, cardiac dysrhythmia, heart pump failure, ischemic or hemorrhagic stroke, chronic kidney disease, chronic kidney failure, and the need for replacement treatment of kidney function with permanent dialysis [5,6]. In patients with hyperlipidemia and extreme exogenous obesity (i.e., the metabolic syndrome) or with diseases such as systemic lupus erythematosus, scleroderma, chronic autoimmune vasculitis, and polyarteritis nodosa, the chances of long-term cardiovascular and/or renal complications are greater [7]. The common characteristic of the postpartum torpid evolution is refractory or rebellious hypertension to the usual management and its consequences, so drug therapy is a priority [1,3,5-8]. The reports of the pharmacological management are scarce, this study **aimed** to analyze the results of the management of postpartum arterial hypertension in patients with SP of a high specialty hospital of Mexico City.

2. MATERIAL AND METHODS

This is an observational, longitudinal, retrospective and analytical study, was carried out in a series of 91 pregnant patients admitted to the Intensive Care Unit (ICU) of the High Specialty Medical Unit (Gynecology and Obstetrics Hospital No. 3, National Medical Center "La Raza" Mexican Institute of Social Security (IMSS), Mexico City) in the period from May 1 to September 30, 2019.

First, the ICU admissions registry and files were consulted to identify pregnant patients with an established diagnosis of SP, compared with the Mexican Clinical Practice Guide (CPG) for preeclampsia, which governs the institutional regulations of the IMSS [9]. For the study, patients of any age, parity, comorbidities and with termination of gestation and with the immediate and mediate puerperium in the same hospital facilities were included. Patients with incomplete or non-existent clinical records, nursing notes and medical indications were excluded. The study began with the admission of patients to the ICU and ended on day 7 postpartum. That is, it included gestational termination, the immediate and mediate puerperium. The general data of the selected patients such as age, parity, comorbidities, gestational age, reasons for gestational termination, route of care at birth, estimated intrapartum bleeding, reinterventions, hypertensive crisis, complications in the puerperium (HELLP syndrome, ischemic or hemorrhagic stroke, eclampsia, hepatic hematoma, acute kidney injury, disseminated intravascular coagulation, etc.), ICU stay, hospital stay and mortality were consulted from the files.

For research purposes, systolic blood pressure (SBP), diastolic blood pressure (DBP) and antihypertensive therapy were studied at four moments; when the patients were admitted to

the ICU with pregnancy (prepartum, baseline measurement) and on days 1, 3 and 7 of the postpartum period. Hypertension was defined as blood pressure $\geq 140/90$ mmHg. It was considered controlled when the blood pressure was $< 140/90$ mmHg. Additionally, the frequency of patients with blood pressure $\geq 140/90$ and $\geq 160/110$ mmHg in the four measurements was also studied, because these values are the cut-off points for hypertensive dyscontrol associated with cerebral, renal, and cardiovascular complications of hypertension [9].

2.1 Data analysis

Descriptive statistics (mean, median, standard deviation, range) and inferential statistics (Student's t test, two-way ANOVA test) were used for the statistical analysis. The value $P = .05$ was considered significant. The statistical program SPSS version 20 was used.

3. RESULTS AND DISCUSSION

3.1 General dates

The mean age was 30.91 ± 6.69 years (limits 14 to 41), the median of parity 2 (limit 1 to 7) and the mean of pregnancy 32.48 ± 4.21 weeks (limits 20 to 40). It was found that 35.16% (32 cases) had HELLP syndrome in the prepartum period and 2.19% (2 cases) with eclampsia. HELLP syndrome and eclampsia were found simultaneously in 1.09% (1 case).

Regarding comorbidities, the overall frequency was 40.65% (37 cases) with the following distribution: one comorbidity 31.87% (29 cases), two comorbidities 6.59% (6 cases) and three comorbidities 2.19% (2 cases). The most frequent comorbidities were: chronic arterial hypertension 25.27% (23 cases), gestational diabetes 8.79% (8 cases), primary hypothyroidism 5.49% (5 cases), non-terminal chronic kidney disease 3.29% (3 cases), heart disease 3.29% (3 cases), type 1 diabetes mellitus 2.19% (2 cases), type 2 diabetes mellitus 1.09% (1 case), systemic lupus erythematosus 1.09% (1 case), gestational hypertension 1.09% (1 case), rheumatoid arthritis 1.09% (1 case), and epilepsy 1.09% (1 case). For gestational termination, cesarean section was used in 94.51% (86 cases) and the vaginal route in 5.49% (5 cases). The mean estimated intrapartum bleeding was 482.58 ± 454.09 ml (limits 50 to 4,000). A reintervention for bleeding was registered in 4.39% (4 cases). The stay in the ICU was 2.33 ± 2.12 days (limits 0.16 to 10.16), hospital stay 7.23 ± 3.69 days (limits 3 to 23) and mortality 0%.

3.2 Blood pressure measurements

When the means of the SBP and DBP of days 1, 3 and 7 postpartum were compared with the baseline measurement, a sustained reduction in the values of both pressures was found.

Figure 1

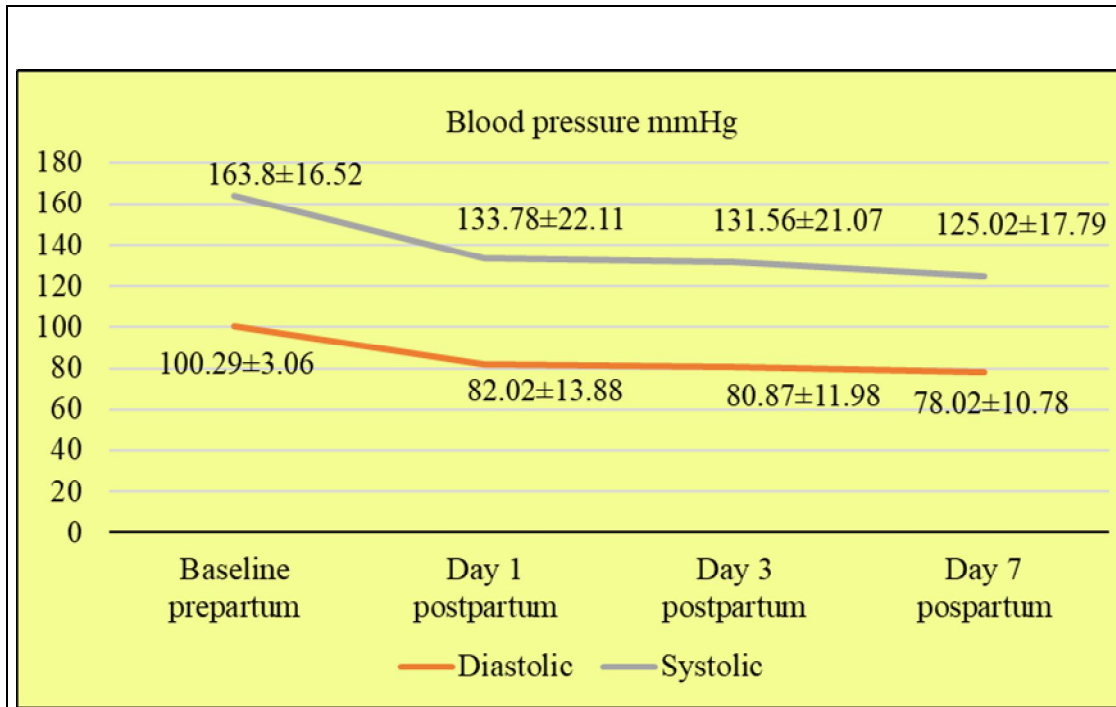


Figure 1. Blood pressure values of 91 patients with severe preeclampsia in the four measurements of the study: baseline (prepartum) and on days 1, 3 and 7 postpartum.

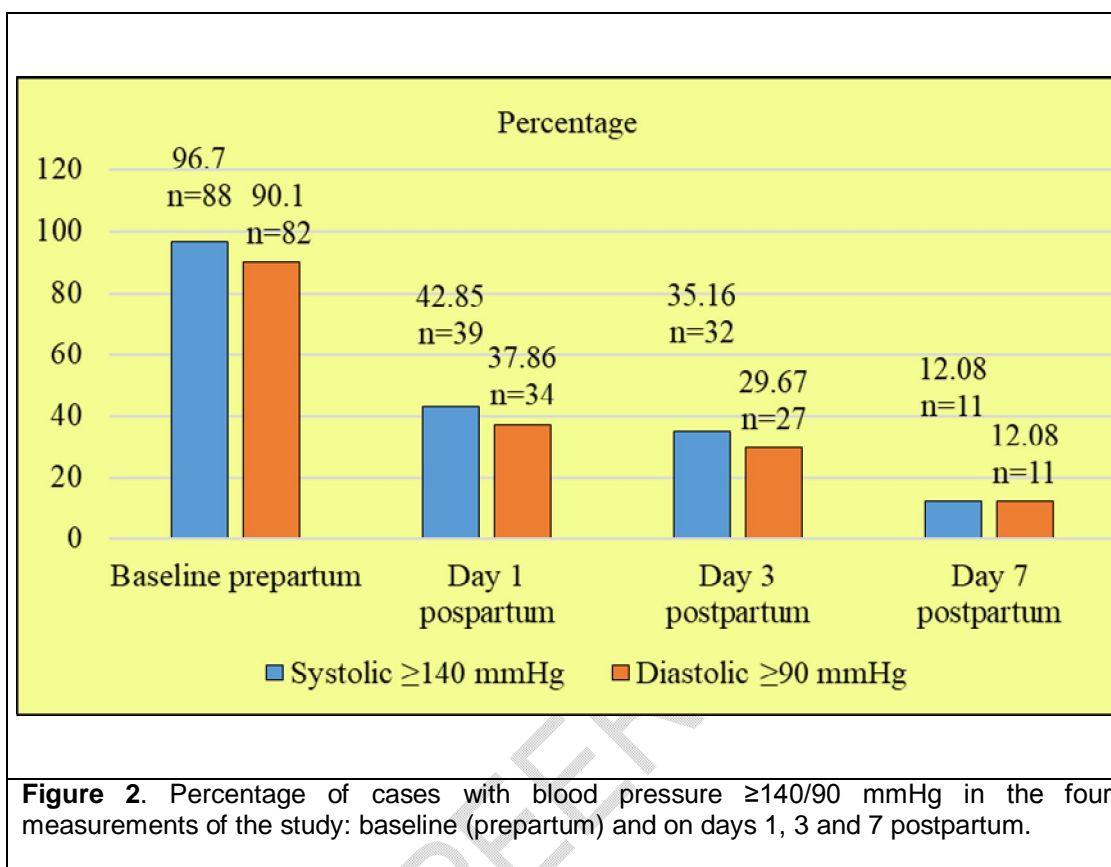
With the two-way ANOVA test, it was found that the decrease in SBP had statistical significance only for the values of day 7, no significance for day 1 and significance considered as borderline for postpartum day 3. **Table 1** As can be seen, even though DBP was also reduced in all postpartum measurements, it did not reach statistical significance.

Table 1. Arterial pressure in 91 patients with severe preeclampsia

Arterial pressure mmHg	Measurements				Value <i>P</i>
	prepartum	postpartum			
	baseline	day 1	day 3	day 7	
systolic	163.08±16.52	133.78±22.11	131.56±21.07	125.02±17.79	^a .15 ^b .05 ^c .007
diastolic	100.29±3.06	82.02±13.88	80.87±11.98	78.02±10.78	^a .61 ^b .11 ^c .14

^a baseline measurement vs day 1, ^b baseline measurement vs day 3, ^c baseline measurement vs day 7

The percentage of patients with blood pressure $\geq 140/90$ mmHg was reduced in the measurements in a uniform way, at the end of the study only 12.08% (11 cases) of them showed hypertension values. **Figure 2**



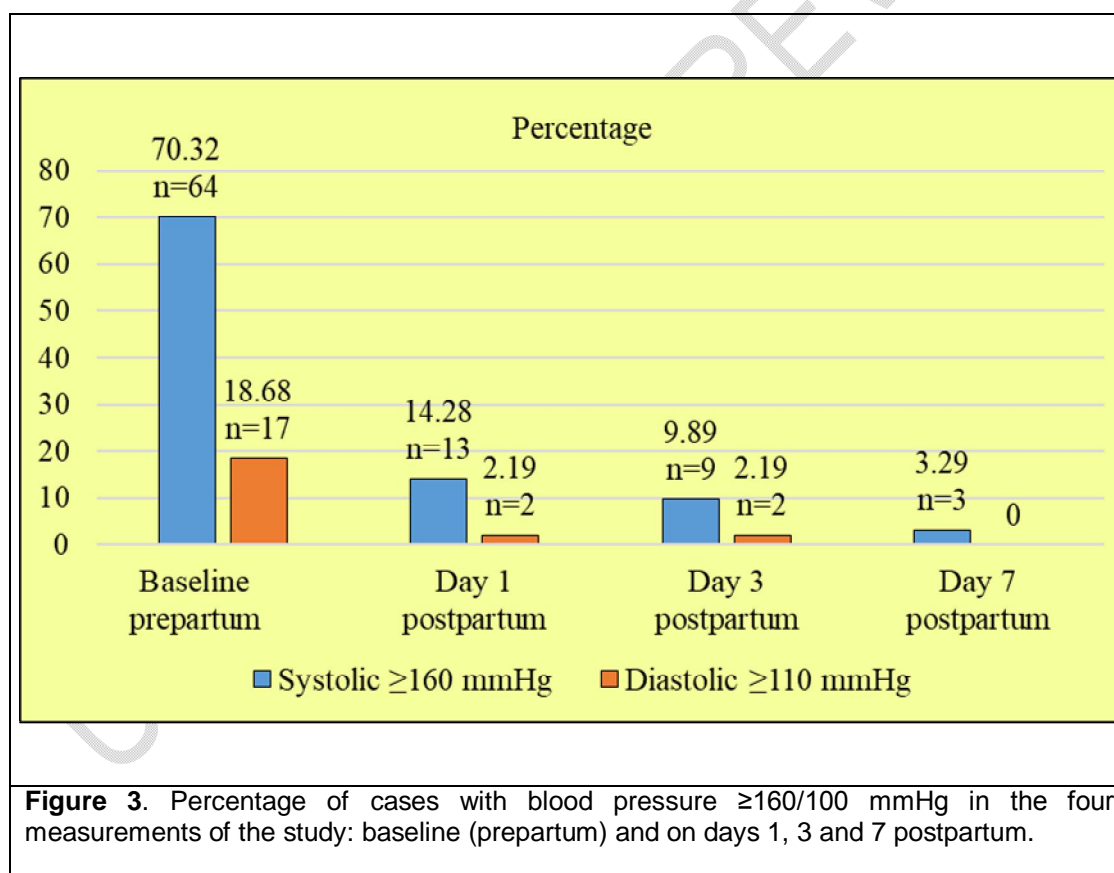
The changes were not statistically significant when compared with the baseline blood pressure. **Table 2**

Arterial pressure	Measurements				Value P
	prepartum	postpartum			
	baseline	day 1	day 3	day 7	
	96.7	42.85	35.16	12.08	
	n=88	n=39	n=32	n=11	
	90.1	37.86	29.67	12.08	
	n=82	n=34	n=27	n=11	

systolic ≥140 mmHg mean	96.70% n=88 164.32±15.31	42.85% n=39 154.12±15.60	35.16% n=32 154.31±14.77	12.08% n=11 150.09±11.75	^a .15 ^b .53 ^c .07
diastolic ≥90 mmHg mean	90.10% n=82 102.48±11.55	37.36% n=34 96.08±9.21	29.67% n=27 94.66±6.13	12.08% n=11 92.72±4.67	^a .61 ^b .11 ^c .14

^a baseline measurement vs day 1, ^b baseline measurement vs day 3, ^c baseline measurement vs day 7

When the frequency of patients with blood pressure ≥160/110 mmHg was compared in the four measurements of the study, it was found that SBP ≥160 mmHg had a higher frequency than DBP ≥110 mmHg. There was a significant reduction in the percentage of hypertensive patients from postpartum day 1 for both pressures. **Figure 3**



At the end of the study, a minimal number of patients continued with SBP ≥160 mmHg (3.29%, 3 cases), but none with DBP ≥110 mmHg. All three patients had chronic hypertension. **Table 3**

Table 3. Frequency and distribution of cases with arterial pressure $\geq 160/110$ mmHg

Arterial pressure	Measurements				Value <i>P</i>
	prepartum	postpartum			
	baseline	day 1	day 3	day 7	
systolic ≥ 160 mmHg	70.32% n=64	14.28% n=13	9.89% n=9	3.29% n=3 *	^a .94 ^b .44 ^c .58
mean	170.66 \pm 12.35	170.38 \pm 16.34	174 \pm 11.74	166.66 \pm 5.77	
diastolic ≥ 110 mmHg	18.68% n=17	2.19% n=2	2.19% n=2	0% -----	^a .64 ^b .48 ^c ----
mean	118.75 \pm 15.54	123.5	110	-----	

^a baseline measurement vs day 1, ^b baseline measurement vs day 3, ^c baseline measurement vs day 7, * All three patients had chronic hypertension.

3.3 Pharmacological management

When the number of antihypertensive drugs used in each of the four measurements of the study was reviewed, it was found that the most frequent was the administration of the combination of three drugs, two drugs and only one drug in that order. On day 7 postpartum, the administration of no medication was predominant (47.25%, 43 cases) followed by two (15.38%, 14 cases), three (13.18%, 12 cases), four (9.89%, 9 cases) and five drugs (8.79%, 8 cases), respectively. **Table 4**

Table 4. Antihypertensive agents administered in the 91 patients with severe preeclampsia.

Measurements	Number of drug per day					
	none	one	two	three	four	five
baseline prepartum	0	25.27% n=23	35.16% n=32	27.47% n=25	8.79% n=8	3.29% n=3
day 1 postpartum	1.09% n=1	31.86% n=29	36.26% n=33	23.07% n=21	3.29% n=3	4.39% n=4
day 3 postpartum	1.09% n=1	23.07% n=21	42.85% n=39	17.58% n=16	7.69% n=7	7.69% n=7
day 7 postpartum	47.25% n=43	5.49% n=5	15.38% n=14	13.18% n=12	9.89% n=9	8.79% n=8

In the baseline measurement, the most prescribed medications were methyldopa tablets 500 mg with 76.92% (70 cases) followed by hydralazine tablets 50 mg 63.73% (58 cases), nifedipine extended-release tablets 30 mg 37.36% (34 cases), hydralazine bolus 5 mg intravenous (IV) 36.26% (33 cases) and metoprolol tablets 100 mg 6.59% (6 cases). The

most popular drugs for prescribing on days 1, 3, and 7 postpartum were nifedipine extended-release tablets, metoprolol, prazosin, and hydrochlorothiazide. Enalapril and losartan were used only in the postpartum period and with regular frequency, but always less than 26%. No cases with adverse effects were documented. **Table 5**

Table 5. Prescription of antihypertensive drugs.

Drugs, daily dose	Measurements			
	baseline	day 1	day 3	day 7
Methyldopa tablets 500 mg	76.92% n=70	6.59% n=6	4.39% n=4	--- ---
Hydralazine tablets 50 mg	63.73% n=58	7.69% n=7	5.49% n=5	4.39% n=4
Nifedipine extended-release tablets 30 mg	37.36% n=34	93.40% n=85	95.60% n=87	52.74% n=48
Hydralazine bolus 5 mg intravenous	36.26% n=33	1.09% n=1	2.19% n=2	--- ---
Metoprolol tablets 100 mg	6.59% n=6	38.46% n=35	49.45% n=45	31.86% n=29
Enalapril tablets 10 mg	----- -----	15.38% n=14	25.27% n=23	20.87% n=19
Prazosin tablets 5 mg	----- -----	14.28% n=13	18.68% n=17	24.17% n=22
Losartan tablets 50 mg	----- -----	6.59% n=6	17.58% n=16	18.68% n=17
None	----- -----	2.19% n=2	2.19% n=2	45.05% n=41
Hydrochlorothiazide tablets 25 mg	----- -----	1.09% n=1	7.69% n=7	13.18% n=12

None of the patients offered the mother's breast to the newborns.

3.4 Discussion

Along with Canada and the United States of America, Mexico is part of the North American region where preeclampsia is considered a permanent health problem for women of reproductive age who achieve pregnancy. All three countries widely recognize that hypertensive disorders of pregnancy are associated with increased maternal morbidity and mortality [9-11]. Most research studies in the region have focused on prenatal and intrapartum complications, so there is little information on postpartum hypertension in preeclampsia and its management. Pharmacological management of high blood pressure is the cornerstone for women complicated with preeclampsia during pregnancy and the puerperium because maternal hypertensive disorder does not end with gestational termination in all cases. Evidence indicates that postpartum hypertension is a window of opportunity for chronicity and its complications [9-12].

In our country, Romero et al. [7] conducted a study from 2007 to 2009 in 153 pregnant patients with preeclampsia. The persistence of preeclampsia and its progression to chronic hypertension were studied through follow-up for 12 weeks after delivery. It was found that 6.6% of the cases persisted with hypertension after the follow-up period. In the report the description of drug management was not included. In the present investigation, the arterial pressure and antihypertensive management were studied in the pregnant state and in the

immediate and mediate puerperium of 91 patients with SP from a tertiary care center in Mexico City. Most of the patients were in their fourth decade of life and their second pregnancy, which, most often, was far from term. A high percentage of HELLP syndrome (35.16%) was documented, but not eclampsia (2.19%). In this series of cases, comorbidities occurred with high frequency (40.65%), the main comorbidity was chronic arterial hypertension (25.27%), this situation may explain the severity of hypertension and the need to use combinations of antihypertensive agents for your control.

The obstetric data showed some peculiarities. For example, the high percentage of caesarean sections for termination of pregnancy (94.51%), the low number of cases with obstetric hemorrhage and reinterventions (4.39%) with 0% mortality, and the short stay in the ICU (mean 2.33 ± 2.12 days) are data that reveal the adequate surgical and medical management in the ICU. However, the hospital stay (7.23 ± 3.69 days) was prolonged because it was conditioned by the difficult control of arterial hypertension.

Not all patients had arterial hypertension $\geq 140/90$ mmHg in the baseline measurement because they had received antihypertensive drugs in their primary and secondary care centers. **Table 2, Figure 2** Only some reached the preeclampsia severity cut-off point $\geq 160/110$ mmHg (**Table 3, Figure 3**), a situation for which international and Mexican experts recommend aggressive and rational management [4-6,9-11]. In them it was found that blood pressure was very high in the baseline measurement (SBP 170.66 ± 12.35 and DBP 118.75 ± 15.54 mmHg), at the end of the study, blood pressure was reduced, but the changes did not show statistical significance (SBP $P=.58$, DBP $P=.48$). Three patients had chronic hypertension. **Table 3**

The analysis of the data has allowed to identify 11 patients (12.08%) with blood pressure $\geq 140/90$ mmHg at the end of the investigation, for this reason they should be considered as a high-risk group. **Table 2, Figure 2** The studies to determine the cause of hypertension refractory to delivery and pharmacological management were not performed at the hospital where the research was conducted. The patients were sent to their primary and secondary care center, it is unknown if the studies were carried out and the results. Uncontrolled hypertension cannot be attributed as a failure of pharmacological management because comorbidities may be involved, mainly chronic hypertension. Special studies to investigate the cause and a follow-up period longer than 7 days are necessary for this select group of patients.

The combination of two, three or more antihypertensive drugs throughout the study and the long hospital stay were necessary due to the difficult control of blood pressure. While they were pregnant (baseline measurement), the patients received oral antihypertensive drugs in 100% of the cases, the most frequent being the combination of two or three drugs, but not monotherapy (25.27%) or polypharmacy (four drugs 8.79%, five drugs 3.29%). **Table 4, Table 5**

For the task force that developed the Canadian CPG, there are insufficient data to decide whether or not antenatal antihypertensive agents should be continued in the postpartum period and which one to choose [10]. They cite the research of Daskalopoulou et al. [13] to recommend the treatment of severe antenatal or postpartum hypertension in all cases with a goal of blood pressure $< 140/90$ mmHg in women with some comorbidity condition and $< 130/80$ mmHg in patients with pregestational diabetes mellitus. The opinion of the group is that the criteria for choosing an antihypertensive agent is not clear according to the meta-analysis published by Magee et al. [14] in 2012, but the drugs commonly used during pregnancy, as well as captopril and enalapril, may be acceptable postpartum options [15,16]. Always considering breastfeeding, special attention should be paid to preterm newborns with

low weight for gestational age because they may have a poor clearance of drugs and a special susceptibility to their effects. The Canadian group recommends that antihypertensive management should be maintained for at least 2 weeks in cases with preeclampsia and 1 week in patients with gestational hypertension [10,17].

In the review published in 2020, experts from the American College of Obstetricians and Gynecologists (ACOG) in the United States of America [11] recommend the administration of labetalol, intravenous (IV) or intramuscular hydralazine, and immediate-release oral nifedipine for urgent management of blood pressure in pregnancy. Its recommendation in the puerperium is the rational use of non-steroidal anti-inflammatory analgesic drugs (NSAIDs) for pain management because the inhibition of prostaglandin synthesis can limit vascular dilation, potentiate vasoconstriction and favor sodium retention to renal level which can aggravate the effects of the hypertensive state [11].

The Mexican CPG on preeclampsia [9] recommends immediate management of postpartum hypertension to avoid the onset of eclampsia and serious cardiovascular complications, prolonging it for at least 2 weeks after delivery. In selected patients, its recommendation is drug management for up to 6 weeks and reduce it when blood pressure reaches values between 130-140/80-90 mmHg after 2 weeks of administration. During pregnancy, oral methyldopa, immediate-release nifedipine, metoprolol, and hydralazine are recommended as first-line drugs and sublingual immediate-release nifedipine, IV labetalol, and IV hydralazine as second-line drugs.

Specifically, at the hospital hosting this research, the first line of antihypertensive management for preeclampsia is oral drugs. During pregnancy the most used are methyldopa, hydralazine, metoprolol, nifedipine and prazosin, in that order. In the puerperium, methyldopa can be ruled out and the inhibitors of angiotensin converting enzyme II (ACE II) and the antagonists of the receptors of this enzyme (ARA II) can be added. So, the sequence includes: hydralazine, metoprolol, nifedipine, prazosin, enalapril or analogues and losartan or some drug from its group. The second line of therapy for a hypertensive crisis includes IV drugs: hydralazine bolus or infusion, nimodipine and/or any of the available nitrates; isosorbide, nitroglycerin, nitroprusside, respectively [9,13]. For the management of postpartum arterial hypertension, it is preferred to continue antenatal agents. It is local adaptation management with respect to official recommendations using available drugs because agents such as labetalol are not available [9,18].

All the patients in the study received the first-line oral drugs already described and IV hydralazine boluses as the only therapeutic rescue option. **Table 4, Table 5** The research showed successful results judging by better control of arterial hypertension with clear statistical significance on day 7 postpartum, especially for SBP values ($P=0.007$), but not for DBP. **Figure 1, Table 1** It was also found that the administration of IV boluses of hydralazine was necessary in a high percentage only in the baseline measurement (36.26%), but not during the puerperium in which the reduction in the number of combined medications was gradually progressive and safe because it was not episodes of hypertensive crisis were recorded. Prazosin, a vasodilator agent that blocks alpha adrenergic receptors with a recommendation not entirely accepted in preeclampsia, was used only in the postpartum period with an increased frequency as the days and measurements progressed (day 1 14.28%, day 3 18.68% and day 7 24.17%) without any collateral effects. **Table 5**

Hydrochlorothiazide, a thiazide diuretic that no evidence-based guideline has recommended in the past or currently for the management of postpartum hypertension in preeclampsia [9-11] was used in a low percentage, it appeared in the registry on day 3 (7.69%) and day 7 (13.18%). **Table 5** Outside of the experience of the treating medical team, its application has

no scientific support, since the last decade it has been known that thiazide diuretics do not reduce the risk of preeclampsia (RR 0.68; 95% CI 0.45-1.03) or improve any other aspect of its evolution [19]. Similarly, furosemide does not have a place in the pharmacological treatment of preeclampsia [20]. In this series, the prescription of hydrochlorothiazide can be considered as a deviation from the normative management of patients [9,18]. Additionally, all the antihypertensive drugs received by the patients in our series are considered by the experts of the European Society of Cardiology and the European Society of Hypertension as usually compatible with breastfeeding. However, no patient offered breast-feeding to the newborns [21].

Romero et al. [7] found 6.6% of patients with postpartum arterial hypertension after 12 weeks of follow-up and in the present study 12.08% of patients were registered in the same condition on day 7 postpartum. Of these, 3.29% (3 cases) were discharged from the ICU with uncontrolled SBP, a relevant situation because it has been identified as the potential responsible for eclampsia and hemorrhagic-type cerebral vascular events, two of the leading causes of maternal death postpartum [22-25]. In this select group of patients who are resistant to pharmacological management, a study protocol is needed aimed at understanding the origin of hypertension. It is also recommended to prolong its clinical follow-up to identify the evolution towards improvement or chronicity and its consequences [26-29]. In this regard, Henry et al. [30] recommend a 12-month follow-up after hypertensive pregnancy to implement strategies related to diet and lifestyle changes.

The main strengths of the research were the determination of the effect of pharmacological management on SBP and DBP in the postpartum stage and the identification of a select group of patients with an unsatisfactory response to management. The weaknesses of the study are related to its design, it was a retrospective investigation of a series of cases with a follow-up of only 7 days postpartum in which no studies were carried out to determine the cause of the persistence of hypertension. The need for additional research to determine the outcome is evident.

4. CONCLUSION

Pharmacological management of postpartum hypertension in the patients studied significantly reduced SBP, but not DBP. The combination of antihypertensive agents was necessary to control blood pressure in most cases. However, a significant group of patients continued to have uncontrolled hypertension at the end of the study.

CONSENT

It is not applicable.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

The study was previously approved by the local health research committee no. 3504 of the host hospital (Registry: R-2018-3504-038).

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