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Original Paper

Use of the Cardiovascular Polypill in Secondary Prevention of Cerebrovascular Disease: A Real-Life Tertiary Hospital Cohort Study of 104 Patients

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Adherence · Stroke · Polypill · Prevention

Abstract
Background: The use of the cardiovascular polypill, a fixed-dose combination treatment, is conceived to improve adherence. However, randomized controlled trials (RCTs) may overestimate it. Studies focusing on cerebrovascular disease and real-life efficacy compared with conventional treatment are lacking. ***Methods:*** This is a retrospective, hospital-based cohort study of acute ischaemic stroke patients who were prescribed a polypill (aspirin 100 mg, atorvastatin 20/40 mg, ramipril 2.5/5/10 mg) versus conventional treatment (aspirin 100 mg and other blood pressure/lipid-lowering agents) in secondary prevention (2017–2018). Clinical records were reviewed 90 days after discharge for stroke recurrence, vascular risk factor control, and safety. Adherence was assessed using the adapted Morisky-Green scale. ***Results:*** A total of 104 patients were included (61% male; mean age 69.7 ± 13.9 years); 54 were treated with the polypill and 50 with conventional treatment. No baseline differences in clinical or demographic variables were detected. No recurrences were registered in the polypill group, compared to 1 recurrence in the conventional treatment group. A significant reduction of systolic blood pressure (SBP) was achieved in the polypill group (12.1 mm Hg) compared to the conventional treatment group (6.8 mm Hg) (p = 0.002). No significant differences were detected regarding the goal of LDL cholesterol ≤70 mg/dL (41 vs. 44%). The adverse events were mild and their frequency was similar in the two groups (9 vs. 2%, ns). Adherence was similarly good in the

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two groups (93 vs. 88%, ns). Polypill group adherence was similar to that reported in a previous meta-analysis of RCTs (93 vs. 84%, ns). ***Conclusion:*** In our experience, the cardiovascular polypill achieved a higher reduction in SBP levels and was well tolerated. Adherence was similar to that found in the previous literature, which is remarkable given the real-life setting of our study.

Introduction

Ischaemic stroke is one of the leading causes of death worldwide, and it is associated with high morbidity due to neurologic disability, psychological and social consequences, and risk of recurrence. On average, the risk of recurrence after an ischaemic stroke or transient ischaemic attack is 3–4%. This risk is highest within the first 90 days after the cerebrovascular event, but it varies widely depending on patients' baseline characteristics and the degree of control of vascular risk factors (VRFs) [1, 2]. Control of VRFs may be challenging for many reasons, especially low adherence, due to the chronicity of the disease, co-payment costs, high pill burden, or the absence of educational programs addressed to patients and physicians [3]. Adherence to secondary prevention treatment amongst patients with cardiovascular disease has shown to improve outcomes and decrease mortality [4]. One of the strategies for improving adherence is the use of fixed-dose combination treatments or polypills, which have proven useful to control VRFs in several studies [5–16].

In Europe, the first commercialized polypill for secondary cardiovascular prevention contains 100 mg of acetylsalicylic acid (ASA), 20 or 40 mg of atorvastatin, and 2.5, 5 or 10 mg of ramipril. These components have proven effective in reducing mortality from cerebrovascular diseases [14–17]. A consensus document about the use of the cardiovascular polypill developed by neurologists was published [18]. According to the document, the polypill could be used in patients with atherothrombotic stroke, lacunar stroke, and cryptogenic stroke and VRFs either if they had previously taken the three separate components or "de novo" after hospital discharge [18].

Multiple clinical trials have demonstrated that the polypill is effective in reducing VRFs when compared to its separate components, and some studies proved that the polypill significantly increased therapy adherence [5–16]. However, the proportion of patients with cerebrovascular diseases included in those studies was low. Moreover, randomized controlled trials (RCTs) may overestimate adherence. Positive results in reducing blood pressure (BP) and LDL cholesterol (LDLc) levels in a real-life setting study of patients treated with the polypill were recently published, but no conventional treatment group was included [19]. To our knowledge, this is the first real-life cohort study to evaluate cardiovascular polypill effectivity, safety, and adherence in patients with cerebrovascular diseases.

Methods

Our observational retrospective cohort study was conducted in consecutive patients admitted due to ischaemic stroke to the neurology department of our tertiary university hospital from January 2017 to January 2018. Patients who received treatment with the cardiovascular polypill (ASA 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5/10 mg) or conventional treatment (ASA 100 mg and other BP-lowering/lipid-lowering agents) in secondary prevention were enrolled. Eligible patients were adult (no upper age limit) and functionally independent before the stroke.

All patients were systematically assessed on discharge and 90 days after the stroke as part of clinical routine at our centre. The doses of ramipril and atorvastatin were decided on based on BP and LDLc levels. The group under conventional treatment received a different treatment for hypertension, which included angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, or thiazides. As for LDLc, the patients in the conventional treatment group received atorvastatin or other lipid-lowering agents such as ezetimibe. The decision on whether to start treatment with the polypill or conventional treatment was made by a vascular neurologist consultant. Patients with a preferential indication for the vascular polypill met some of the following criteria: using polymedication, being elderly, having multiple vascular diseases, being young active workers, or having suspicion for poor adherence to treatment [18].

Baseline features, medical history, clinical evaluation, and laboratory tests were obtained from clinical records completed by neurologists. Stroke severity was measured with the National Institutes of Health Stroke Scale (NIHSS) [20]. The aetiology of the stroke was assessed by performing a thorough study, which included supra-aortic and transcranial vessel Doppler or computed tomography angiography, EKG monitorization, and transthoracic echocardiography. The aetiology of the stroke was defined according to the TOAST classification [21]. Patients were eligible for the study if their stroke was atherothrombotic, a lacunar stroke, or a cryptogenic stroke with VRFs.

A clinical assessment was performed 90 days after the stroke at the Cerebrovascular Disease Clinic. LDLc levels were evaluated from blood tests performed within 2 weeks prior to the clinical assessment, and BP levels were assessed. Goals of BP <140/90 mm Hg and LDLc ≤70 mg/dL were established according to the prevailing guidelines when the enrollment started [1, 22]. Adherence was evaluated using an adaption of the Morisky-Green questionnaire by Val Jiménez [23]. This adapted scale includes four questions: (1) "Some people forget to take their medications, do you do this?" (2) "Some people miss out a dose of their medication or adjust it to suit their own needs, do you do this?" (3) "Some people stop taking their medication when they feel better, do you do this?" and (4) "Some people stop taking their medication when they feel worse, do you do this?" If the answer was negative to every question, the patient was considered to have good adherence. An adaptation of the TSQM-9 questionnaire was used to assess satisfaction in the patients treated with the polypill [24].

The main efficacy outcomes were changes from baseline in BP levels and LDLc levels; the proportion of patients achieving the BP and LDLc goals; and stroke recurrence, safety, and adherence.

Categorical variables are presented as proportions, and continuous variables as mean and standard deviation. The χ^2 test was used to compare categorical variables and, and Student's *t* test for continuous variables. Statistical significance was considered for *p* values <0.05. The analyses were performed using SAS 9.2.

Results

Data from 104 patients were collected: 54 were treated with the polypill (65% male; mean age 67.7 ± 12.8 years) and 50 with conventional medications (56% male; mean age 71.7 ± 14.8 years) (ns). There were no significant differences regarding VRF distribution. The patients' baseline characteristics are summarized in Table 1.

Regarding treatment upon discharge, the doses and treatments received are summarized in Table 2. In the conventional treatment group, only 1 patient received ramipril. The remaining patients received different BP-lowering agents such as other angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and thiazides.

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Table 1. Baseline characteristics

	Polypill	Conventional treatment
Patients, *n* (%)	54 (100)	50 (100)
Mean age ± SD, years	67.7±12.8	71.7±14.8
Male, *n* (%)	35 (64.8)	28 (56)
Vascular risk factors, *n* (%)		
Hypertension	42 (77.8)	32 (64)
Hyperlipidaemia	29 (53.7)	26 (52)
Diabetes mellitus	10 (18.5)	16 (32)
Smoking	24 (44.4)	22 (44)
Previous stroke	1 (1.9)	3 (6)
Previous treatment, *n* (%)		
Antiplatelets	1 (1.9)	9 (18)
BP-lowering agents	34 (63)	28 (56)
Cholesterol-lowering agents	12 (22.2)	18 (36)

SD, standard deviation; BP, blood pressure.

Table 2. Treatment on discharge

	Polypill	Conventional treatment	*p* value
Patients, *n* (%)	54 (100)	50 (100)	
BP-lowering agents, *n* (%)			
Ramipril 2.5 mg	18 (33.3)	1 (24)	
Ramipril 5 mg	14 (25.9)	–	
Ramipril 10 mg	22 (40.1)	–	
Other BP-lowering agents	12 (22.2)	44 (88)	
>1 BP-lowering agent	12 (22.2)	15 (30)	ns
Cholesterol-lowering agents, *n* (%)			
Atorvastatin 20 mg	4 (7.4)	4 (8)	
Atorvastatin 40 mg	50 (92.6)	30 (60)	
Atorvastatin 80 mg	–	6 (12)	
Other cholesterol-lowering agents	–	10 (20)	
>1 cholesterol-lowering agent	–	4 (8)	0.03
Antiplatelets, *n* (%)			
ASA 100 mg	54 (100)	46 (92)	ns
Clopidogrel 75 mg	2 (3.7)	9 (18)	0.02
Double antiplatelets (ASA + clopidogrel)[a]	2 (3.7)	5 (10)	ns

BP, blood pressure; ASA, acetylsalicylic acid. [a] During 21 days.

There were no significant differences regarding the need for more than one BP-lowering agent (22 vs. 30%, ns).

Changes in BP and LDLc levels are summarized in Table 3. BP levels were significantly reduced from a mean of 149.9 to 131 mm Hg ($p < 0.001$), and from 85.5 to 80.4 mm Hg ($p < 0.001$) in the polypill group. LDLc levels were significantly reduced from 109.2 to 79.6 mg/dL ($p < 0.001$) in the group receiving the cardiovascular polypill. The mean reduction in systolic BP (SBP) was significantly higher in the polypill group than in the conventional treatment group, i.e., 12.1 versus 6.8 mm Hg ($p = 0.002$). The goal for BP (<140/90 mm Hg) was achieved by 85 and 74%, respectively (ns), and the goal for LDLc (≤70 mg/dL) was achieved by 41 and 44%, respectively (ns).

Table 3. BP and LDLc levels

	Polypill	Conventional treatment	*p* value
SBP, mm Hg			
At baseline	149.9±12.8	147±20.3	
After 90 days	131±8.3	135.8±13.7	
SBP reduction	12.1 (7.4)	6.8 (9.2)	0.002
DBP, mm Hg			
At baseline	85.5±8.9	81±15.9	
After 90 days	80.4±5.8	76.5±14.1	
DBP reduction	5±11.7	5±9.2	ns
BP goal achievement, *n* (%)	46 (85.2)	37 (74)	ns
LDLc, mg/dL			
At baseline	109.2±27.8	102.2±30.5	
After 90 days (mean + SD)	79.6±24.9	80.3±26.7	ns
LDLc reduction	24.8±21.3	17.3±26.1	ns
LDLc goal achievement, *n* (%)	22 (40.7)	22 (44)	ns

Values denote mean ± SD unless specified otherwise. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDLc, LDL cholesterol; SD, standard deviation.

There were no recurrences or deaths in the polypill group, and 1 recurrence in the conventional treatment group (ns). In the group receiving the cardiovascular polypill, only 5 patients presented with mild adverse events: cough in 2 (3.7%), headache in 1 (1.9%), dizziness in 1 (1.9%), and mild epistaxis in 1 (1.9%). In the conventional treatment group, 1 patient suffered an upper gastrointestinal bleeding (2%) (ns). Ninety-one per cent of the patients were satisfied with the use of the cardiovascular polypill.

Treatment adherence was high in both groups (93 and 88%, respectively) (ns). Adherence among the patients treated with the polypill in our study was similar to that reported in a previous meta-analysis of RCTs [12] (93 vs. 84.3%) (ns).

Discussion

In our study, the effectivity of the cardiovascular polypill was assessed for the first time in stroke prevention in a real-life setting, and compared to a conventional treatment group. Previous clinical trials and a phase IV study support the effectivity of the polypill in improving adherence and controlling VRFs [13, 19]. However, these studies have some limitations: a low proportion of patients with stroke (<15 and 3%, respectively); the likelihood of overestimation of adherence; and heterogeneity in the measurement of adherence. Our study contributes to the literature in several ways.

First of all, real-life studies better represent routine practice compared with clinical trials and can provide valuable information about effectivity, safety, and adherence. It is noteworthy that under real-life conditions a significantly higher reduction of SBP was achieved in the group treated with the polypill than in the conventional treatment group. Importantly, hypertension treatment is the most important intervention for cerebrovascular disease prevention. There were some differences in the type and dose of BP-lowering agents between groups, and a higher number of patients in the conventional treatment group received more than one BP-lowering agent (30 vs. 22%; ns). Consequently, we hypothesize that the significant reduction in SBP in the polypill group might be the result of slightly better adherence.

However, other factors such as the different intensity of BP-lowering agents could have also played a roll.

In addition, LDLc levels were also significantly reduced from baseline. Although the goal of LDL was achieved by 41 and 44%, respectively (ns), the overall results were better than those in previous studies [13, 19, 25]. This suggests that other factors such as a strict diet, the use of more potent statins, and a longer follow-up may play a role in the control of LDLc levels. Moreover, there were no recurrences or severe adverse events among the patients treated with the polypill. Although the sample was too small to draw conclusions about recurrence, these results support the effectivity of the polypill.

Another issue to consider is the double antithrombotic treatment. In this study, 7 patients received double antithrombotic treatment, 2 (3.7%) in the polypill group and 5 (10%) in the conventional treatment group. It is important to remark that this study was conducted before the publication of the POINT trial [26]. Despite the fact that the cardiovascular polypill only contains ASA, it can be prescribed with clopidogrel in order to simplify the therapeutic scheme from 4 pills (ASA, BP-lowering agent, LDLc-lowering agent, and clopidogrel) to 2 pills (polypill and clopidogrel). This could also be applied to other patients with ischaemic stroke and the need for two antiplatelets, such as patients with carotid or intracranial stents.

Another strength of the study is that adherence was measured with a robust and reproducible scale, the adapted Morisky-Green scale. As previously mentioned, results from adherence trials should be interpreted cautiously as behaviour is significantly changed in RCTs, due to the Hawthorn effect and other factors [19, 27]. However, in this study the polypill showed good results of adherence, similar to those in previous studies, in the real-life setting. A feasible explanation for the lack of significant differences between groups may be attributed to the fact that treatment was started after hospitalization. At that time and during the following months, patients may be more aware of the disabling consequences of stroke recurrence. Consequently, it may occur that differences between groups become significant and more favourable to the use of the polypill after a longer follow-up, as observed in other studies [13].

This study presents some limitations that should be taken into account, such as its relatively small sample size and the heterogeneity of treatment in the conventional treatment group. Although it was not a randomized study, the baseline characteristics were similar in the two groups. Nevertheless, the indication for the use of cardiovascular polypill was decided by a vascular neurologist, taking into account some patients' characteristics. Consequently, the final analysis may have been subject to selection bias. This may limit the generalizability of the results. One can argue that the follow-up of 90 days was short. However, this is the period of highest risk for recurrence after a stroke. Moreover, a longer follow-up may demonstrate better adherence among patients treated with the polypill, as well as better outcomes in the control of VRFs.

Conclusion

In our experience, the cardiovascular polypill was well tolerated, induced good adherence, and proved to be useful for the prevention of recurrent stroke after hospital discharge, mainly due to better lowering of BP. Regular assessment of BP and LDLc levels is mandatory in order to optimize treatment and prevent vascular events.

Statement of Ethics

The subjects (or their parents or guardians) have given their informed written consent, and the study protocol was approved by the steering committee of Ramon y Cajal University Hospital (Comité Ético de Investigación Clínica, CEIC 179/18).

Conflict of Interest Statement

V. Ros-Castelló has received travel grants from Ferrer Laboratories, and J. Masjuan provided consultation to Ferrer Laboratories.

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Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by V. Ros-Castelló, A. Gómez-López, A. Sánchez-Sánchez, and J.L. Chico-García. Analysis was performed by V. Ros-Castelló, E. Natera-Villalba, and A. Alonso-Canovas. The first draft of the manuscript was written by V. Ros-Castelló, E. Natera-Villalba, A. Alonso-Canovas, and J. Masjuan, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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