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Original article

Efficacy of a Combined Strategy to Improve Low-density Lipoprotein Cholesterol Control Among Patients With Hypercholesterolemia: A Randomized Clinical Trial

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ABSTRACT

Introduction and objectives: Several interventions can improve low-density lipoprotein cholesterol (LDL-C) control. Our main objective was to evaluate the efficacy of a combined intervention to improve LDL-C control in patients with hypercholesterolemia. The study also assessed the efficacy of the intervention in improving adherence (pharmacological, diet, and exercise).

Methods: A multicenter, parallel group, randomized clinical trial (primary care) was conducted in 358 adults diagnosed with hypercholesterolemia, whether receiving prior drug therapy or not. We compared 178 participants who received the combined intervention (written material, self-completed registration cards, and messages to mobile telephones) with 178 controls. The main outcome variable was the proportion of participants with adequate LDL-C control (target levels of the European guidelines on dyslipidemia and cardiovascular risk) at 24 months.

Results: At 24 months, the mean reduction in LDL-C was significantly higher in the intervention group (23.8 mg/dL [95%CI, 17.5-30.1]) than in the control group (14.6 mg/dL [95%CI, 8.9-20.4]; $P = .034$). The mean LDL-C decrease was 13.1% ± 28.6%. At 1 year, the proportion of participants with adequate control was significantly higher in the intervention group than in the control group (43.7% vs 30.1%; $P = .011$; RR, 1.46). Adherence was significantly higher in the intervention group, both to drug therapy (77.2% vs 64.1%; $P = .029$) and exercise (64.9% vs 35.8; $P < .001$), but not to diet.

Conclusions: The combined intervention significantly reduced LDL-C (by more than 13% at 2 years) and improved the degree of LDL-C control in patients with hypercholesterolemia at 1 year.

Eficacia de una estrategia combinada para mejorar el control del colesterol unido a lipoproteínas de baja densidad en pacientes con hipercolesterolemia. Ensayo clínico aleatorizado

Palabras clave:
Hipercolesterolemia
Cumplimiento terapéutico
Atención primaria de salud
Ensayo clínico

RESUMEN

Introducción y objetivos: Intervenciones diferentes pueden mejorar el control del colesterol unido a lipoproteínas de baja densidad (cLDL). El objetivo principal era evaluar la eficacia de una intervención combinada para mejorar el control del cLDL de pacientes con hipercolesterolemia. También se evaluó su eficacia para mejorar el cumplimiento (farmacológico, dieta y ejercicio).

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Métodos: Ensayo clínico aleatorizado, de grupos paralelos y multicéntrico (atención primaria) que incluyó a 358 adultos diagnosticados de hipercolesterolemia con tratamiento previo farmacológico o no. Se comparó a 178 sujetos que recibieron intervención combinada (material escrito, tarjetas autocumplimentadas y mensajes al móvil) frente a 178 controles. La variable principal de resultado fue la proporción de sujetos con adecuado control del cLDL (valores recomendados en las guías europeas de dislipemias y riesgo cardiovascular) a los 24 meses.

Resultados: El grupo de intervención mostró una reducción media del cLDL significativamente superior a los 24 meses respecto al control, 23,8 mg/dl (IC95%, 17,5-30,1) y 14,6 mg/dl (IC95%, 8,9-20,4), respectivamente (p = 0,034). El promedio de la reducción del cLDL fue del 13,1 ± 28,6%. La proporción de sujetos con adecuado control al año fue significativamente superior en el grupo de intervención (43,7 frente a 30,1%; p = 0,011; RR = 1,46). En el grupo de intervención, el cumplimiento farmacológico fue significativamente superior (77,2 frente a 64,1%; p = 0,029) y de la práctica de ejercicio (64,9 frente a 35,8%; p < 0,001), aunque no de la dieta.

Conclusiones: La intervención combinada consigue una reducción significativa de las cifras de cLDL (superior al 13% al cabo de 2 años) y mejora el grado de control de pacientes con hipercolesterolemia al año.

Abbreviations

CVR: cardiovascular risk
LDL-C: low-density lipoprotein cholesterol
TC: total cholesterol

INTRODUCTION

The prevalence of hypercholesterolemia in Spain ranges from 20% to 50%, depending on the plasma cholesterol concentrations considered.[1,2]

For better cholesterol control in patients with hypercholesterolemia, experts agree on the benefits of diet, physical exercise, and drug therapy in primary prevention and, particularly, secondary prevention.[3–5] Nonetheless, despite the recommendations and new lipid-lowering agents, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels exceed the recommended targets in both Spain and Europe.[2,6–9]

One of the factors limiting target achievement in hypercholesterolemic patients is nonadherence to treatment, which affects both medication use and lifestyle recommendations.[10]

To address this situation, various strategies have been used to improve adherence and thus lipid parameter control in these patients. In patients with risk factors such as hypertension, adherence has been improved through a combination of written material, telephone calls, and mailed information on the disease.[11,12] In individuals with dyslipidemia, adherence has been improved through telephone reminders[13,14] and cards containing treatment information.[15] Studies on adherence in dyslipidemia indicate that improvements are required in both drug adherence and adherence to the other recommendations to achieve control targets.[10]

Given that combined strategies to improve adherence show better results than individual interventions,[16,17] we planned a strategy including interventions with proven ability to improve adherence.[13–15] Thus, the main aim of this study was to evaluate the efficacy of an intervention to improve the degree of control in hypercholesterolemic patients involving a strategy combining delivery of written information, text messages, and registration cards for the degree of adherence as complementary measures to standard clinical care. In addition, the study assessed the ability of the intervention to improve adherence (pharmacological, diet, and exercise).

METHODS

The present randomized, parallel-group, multicenter clinical trial is registered at ClinicalTrials.gov (NCT02314663). Participants were selected from clinics in 8 health care centers in 3 health districts of 3 Spanish autonomous communities: Castile-La Mancha (Albacete), Aragon (Zaragoza), and Galicia (Vigo). We included individuals aged ≥ 18 years previously diagnosed with defined hypercholesterolemia (TC ≥ 250 mg/dL)[18] who were receiving standard treatment (drug-based or not) and attending the participating centers. We excluded patients who were unable to undergo follow-up during the intervention (due to illiteracy or lack of a mobile telephone), had a physical disability impeding participation, or had a severe organic or psychiatric chronic disease precluding follow-up. All individuals signed an informed consent form after receiving a thorough explanation of the study. The study was approved by the Ethics Committee for Clinical Research in the Albacete Health Care Area and was carried out according to the ethics guidelines for clinical trials (Spanish Royal Decree 223/2004) and the Declaration of Helsinki.

The sample size required for the analysis was calculated using a 2-sided test, and a difference of 20% in the proportion of participants achieving lipid control targets was considered clinically relevant: 55% in the control group[19] and 75% in the intervention group. With 90% statistical power and 5% alpha error, a sample size of 155 individuals per group was estimated (310 total). After consideration of an expected patient loss of 15%, the final sample size per group was 179 individuals (total, 358). Of the 379 individuals asked to participate, 21 declined (acceptance rate, 94.5%) (Figure 1). The recruitment period lasted from March to December 2013.

For strategic reasons, 8 basic health care regions of the health districts of Albacete, Zaragoza, and Vigo were chosen for participant selection. To avoid carryover bias, participants in the control and intervention groups were from different areas. Thus, participant randomization was centrally performed according to health care region (Efron randomization) by a researcher who was not involved in the interviews or analysis. Participants were consecutively selected.

Participants in the intervention group received the following: *a)* written information on the disease and its treatment (provided at each visit) (Appendix 1 and Appendix 2 of the supplementary material); *b)* mobile telephone text messages with summaries of recommendations, reminders of dates of next appointments, and notifications of new appointments if any previous ones were missed (during between-visit periods) (Appendix 3 of the

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