Secondary Prevention of Coronary Artery Disease. Flu Vaccinations and New Evidence of the Role of Infection in Acute Coronary Syndromes

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Recent reports have detected an increase in the number of patients with acute coronary syndromes during the flu season. More recently, case-control studies of patients with prior infarction have shown that flu vaccination significantly reduces the risk of myocardial necrosis and strokes.

The World Health Organization recommended flu vaccination for the Southern Hemisphere in the winter of 2001. We evaluated the preventive impact of flu vaccination on subsequent ischemic events in myocardial infarction patients and in subjects undergoing scheduled percutaneous coronary angioplasty.

In the first study we included 200 myocardial infarction patients admitted in the first 72 hours and 100 patients scheduled for angioplasty/stent (PCI) without unstable coronary artery disease, prior bypass surgery, angioplasty or tissue necrosis, were included in a prospective, multicenter registry, during the winter season. Infarction patients received standard therapy, and then were randomly allocated in a single-blind manner as a unique intramuscular Influenza vaccination or as controls. Similarly, PCI patients were allocated to either vaccination or control. The first primary outcome –cardiovascular death– occurred within 6 months in 2% of the patients in the vaccinnated group vs 8% of controls (RR: 0.25; 95% CI, 0.07-0.86; p = 0.01). The triple composite end point occurred in 11% of the patients in the vaccinnated group vs 23% of controls (p = 0.009) at 6 months.

Although our study is the first to demonstrate lower rates of cardiovascular ischemic events in patients vaccinated against Influenza during the flu season, the modification of flu vaccination recommendations in patients admitted for cardiovascular events merits further study before being considered.

Key word: *Influenza. Atherosclerosis. Immune system.*

Prevención secundaria de la cardiopatía isquémica con la vacuna antigripal. Nueva evidencia sobre el papel de la infección y los síndromes coronarios agudos

Ciertas asociaciones, por demás intrigantes, han sido expuestas alrededor de la epidemiología de la enfermedad coronaria. Un ejemplo de ello es la incidencia de infarto de miocardio y muerte cardiovascular observada durante los inviernos y las epidemias de gripe por Influenza. Recientemente, estudios retrospectivos encontraron una franca reducción de infarto de miocardio y cerebral entre aquellos sujetos ateroscleróticos que fueron vacunados en el hemisferio norte contra esta virosis.

Los resultados obtenidos en el primer estudio con antibióticos sugirieron fuertemente que el sistema inmunitario podría estar involucrado en la aterosclerosis como en cualquier situación donde se aplique una terapéutica supresora inmunológica.

El ensayo con una vacuna antigripal de aplicación en una dosis única de la cepa recomendada por la Organización Mundial de la Salud para el invierno transcurrido en el hemisferio sur de 2001, en 200 pacientes coronarios agudos (infarto de miocardio con o sin supradesnivel del segmento ST) y un grupo adicional de 100 sujetos sintomáticos por angina y programados para una intervención de angioplastia transluminal coronaria puso de manifiesto una franca reducción de la mortalidad a 6 meses (2 frente a 8% en controles; RR = 0,25; IC del 95%, 0,07-0,86; p = 0,01).

Si bien la inoculación de las vacunas antigripales sugeridas por los organismos sanitarios es prácticamente inocua, la modificación de políticas sanitarias para la indicación de este tipo de vacunas durante la hospitalización por un accidente cardiovascular quizá merezca un tiempo de reflexión antes de ser finalmente considerada.

Palabras clave: *Influenza. Aterosclerosis. Sistema inmunológico.*

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Lately we have come to understand that some of the phenomena involved in the development of various chronic diseases, like atherosclerosis, can be evidenced by following a path opposite to the one traditionally used in research. From the secondary prevention of a chronic disease we can learn about some of the mechanisms that originate it. This unusual, but ethical, approach even makes it possible to clarify models developed in laboratories and improve them to reproduce the process under study.

For the last 30 years and up to the present, the acute thrombotic phenomenon that is mainly responsible for what are now known as the coronary syndromes dominated the attention of most practicing physicians.

From the original trials of antiplatelet and antithrombotic therapy[1-4] to the megastudies that confirm the effectiveness and safety of these agents, enough time has passed to understand, at least in part, why the recurrence of cardiovascular accidents is far from negligible in the atherosclerotic population in spite of early and effective treatment.

A new myocardial infarction or death occurs in approximately 6 of 100 patients per month To these cases must be added another 6 non-fatal infarctions or deaths for every 100 subjects a year, and revascularization rates rise to 9% from the time that the patient leaves the hospital in an apparently good state of health after suffering a first coronary event and in the next 12 months of follow-up.[5]

The first assumption about the pathological mechanism involved in this overly high rate of reiterative episodes of ischemia was that the same thrombotic phenomenon remains active and capable of inducing thrombin formation days after the initial accident involving the atherosclerotic plaque.[6,7]

Nevertheless, the prolongation of antithrombotic therapy beyond the first days has so far produced inconsistent results.[8] An apparent benefit has been observed with certain drugs, in addition to a high cost in terms of loss of safety.[9]

Even aggressive trials combining antithrombotic therapy and early revascularization procedures, particularly in patients with a suspected high clinical risk,[10] entail an equally high incidence of subsequent events.[11]

If the incidence of cardiovascular accidents obtained from medical records is added to the results of clinical trials, it results in a fair amount of information.

Certain intriguing associations have been found in the epidemiology of coronary artery disease, suggesting that other mechanisms are involved. An example of this is the incidence of myocardial infarction and cardiovascular death observed in winter and during flu epidemics.[12,13]

More recently, Naghavi et al[14] found this association in an observational study of coronary patients seen at the University of Texas during the winter season from October 1997 to March 1998. These investigators found that patients who were vaccinated against flu had a significantly lower risk of a new adverse event than those who were not vaccinated. Similarly, Lavallee et al[15] found that the patients vaccinated with this aim during the epidemiological campaign had lower rates of cerebrovascular accident in the winter of 1999 to 2000 in Paris, France.

This information can be combined with that obtained in models developed at the same time.

An interesting viral theory can explain some of the mechanisms that lead to restenosis and the development of coronary artery disease.[16,17] In immunocompetent subjects, virosis is rarely reactivated with such an aggressive replication rate. In any case, this subject is in a state of «aborted infection» where certain genetic viral products can be regenerated and converted, under certain circumstances, into triggers for viral replication, as in the case of endothelial injury caused by an angioplasty balloon in infected individuals.

These findings make lymphocytic cells of the B line relevant.

It is well known that a large percentage of T lymphocytes in atherosclerotic plaques are «preactivated» in relation to other circulating T cells. In addition, a small proportion of these lymphocytes express certain antigens of cell proliferation or receptor co-stimulation, indicating that they are responding to the presence of other antigenic stimuli.[18] The origin of this stimulation is unknown and not even very clear, although it is evident that the immunological process and infectious process coincide.

In contrast with this cell line, few B lymphocytes are found in the same atherosclerotic plaques. B lymphocytes are activated in the usual way against specific antigens, but rarely spontaneously. This makes it likely that a rapid humoral response, either specific or non-specific, occurs after vaccination, reflecting an immediate migration of subpopulations of these cells that can respond to the stimulus induced.[19] Influenza antibodies are found in peripheral blood one week after the flu vaccination.[20]

In the case of atherosclerosis, the first conception of this phenomenon was indirectly analyzed in an animal model. In 1978, Fabricant et al[21] infected hens with herpes virus, which quickly developed atherosclerotic injuries similar to those seen in humans. Minick et al[22] immediately verified that immunizing them with an attenuated viral load prevented the development of atherosclerosis.

In our original study with macrolide antibiotics,[23] we found that the effect of these medications persisted up to 60 days after therapy stopped.[24]

This phenomenon is commonly observed in any situation in which an immunosuppressive therapy is

TABLE 1. **Primary endpoints at 6 months of follow-up**

	Vaccine group (n=151), No. (%)	Control group (n=150), No. (%)	RR	*P*
Death	3 (2)	12 (8)	0.25 (0.07-0.86)	.01
Triple endpoint	17 (11)	34 (23)	0.50 (0.29-0.85)	.009

Triple primary endpoint indicates combination of rehospitalization, death, and non-fatal infarction.

TABLE 2. **Primary endpoint at 6 months of follow-up in the myocardial infarction group**

	Group A (n=100), No.	Group B (n=100), No.	RR	*P*
Death	2	8	0.25 (0.05-1.15)	.05
Non-fatal reinfarction	4	4	1.00 (0.26-3.89)	
Rehospitalization	4	12	0.33 (0.11-1.00)	.03
Double primary endpoint	6	12	0.30 (0.20-1.28)	.03
Triple primary endpoint	10	24	0.42 (0.21-0.83)	.008

Double primary endpoint indicates cardiovascular death and non-fatal reinfarction; triple primary endpoint, combination of rehospitalization, death, and non-fatal infarction.

applied. When this therapy ceases abruptly, a residual effect persists that benefits the subject, indicating the appearance of immunocompetent states and deficiencies.

This was the rationale for the first trial of a flu vaccine in 200 acute coronary patients (myocardial infarction with or without deviation of the ST segment) and an additional group of 100 symptomatic subjects with angina who were scheduled for transluminal coronary angioplasty but did not have any sort of previous atherosclerotic evidence, in order to avoid reactivating a potentially infectious viral load in subjects undergoing «scheduled endothelial injury.»

TABLE 3. **Primary endpoint at 6 months of follow-up in the group of transluminal coronary angioplasty**

	Vaccine group (n=51) (%)	Control group (n=50) (%)
Death	1	4*
Non-fatal reinfarction	4	4*
PTCA or CABG	3	3*
Triple endpoint	8 (15)	11 (22)*

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; triple primary endpoint, combination of rehospitalization, death, and non-fatal infarction.
* *P* not statistically significant.

The initial results of the Flu Vaccination in Acute Coronary Syndromes (FLUVACS) study[25] were obtained 6 months after a single dose of the strain recommended by the World Health Organization in the southern hemisphere for the winter of 2001,[26] 0.5 ml of the A/Moscow/10/99, A/New Caledonia/20/99 (H1N1) and AB/Sichuan/379/99. The results are shown in Tables 1 to 3.

In the trial, the benefit was confined mainly to the group with myocardial infarction (Table 2; Figure 1). Preliminary speculations on this topic arose from the idea that the nonspecific activation of the B lymphocyte line, beyond a limited number of patients and given the role of probability, acts in an independent way in a frankly unstable clinical situation with probable endothelial injury, as opposed to the circumstances where the absence of clinical instability suggests different state of immunocompetence a priori.

Concomitantly with this clinical study, Dimayuga et al[27] investigated the effects of reconstitution with B cells in immunodeficient mice subjected to an

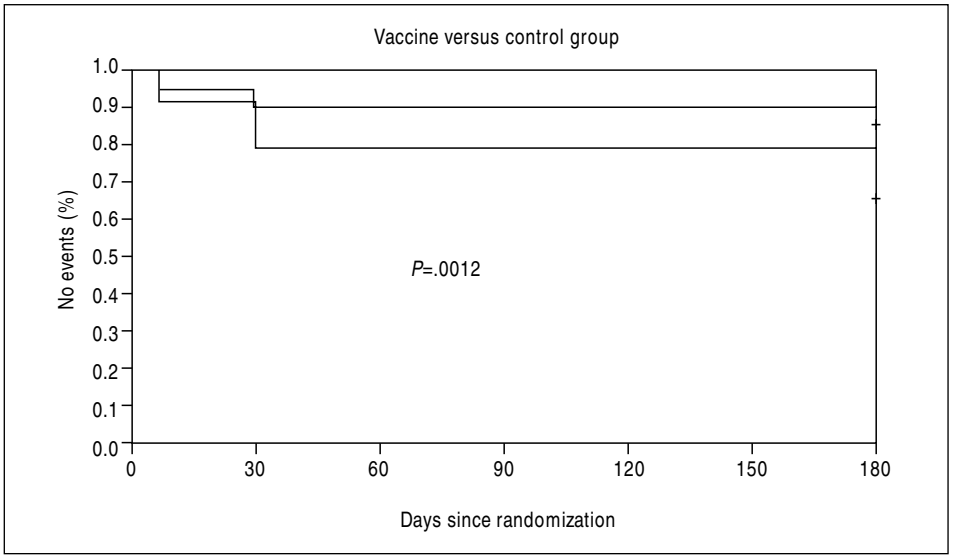

Fig. 1. Patients free of events (%).

endothelial insult. They found that these cells could modulate tissue aggression.

In Sweden, Caligiuri and Hansson[28] found that splenectomy in hypercholesterolemic apo-E deficient mice aggravated the development of atherosclerosis. They later transferred cells from the spleen of these mice to themselves, significantly reducing disease progression.

Bacterial and viral infections can evidently stimulate an immunological reaction through specific and non-specific mechanisms that recall and simulate well-known molecular structures for the maintenance over time of a chronic disease with a strong inflammatory component, as is the case of atherosclerosis.[29]

The conditions that determine how the innate and acquired immunological system finally contributes to the pathogenesis of these conditions have still not been resolved.

Although the administration of a single dose of flu vaccine, as suggested by health-care organizations, is practically innocuous, the modification of health-care policies for this indication during hospitalization for a cardiovascular event probably merits further study.

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