



REVISTA MÉDICA DEL
HOSPITAL GENERAL
DE MÉXICO

www.elsevier.es/hgmx



ORIGINAL ARTICLE

Effect of a single dose of pre-operative pravastatin on C-reactive protein levels and neutrophil/lymphocyte ratio in patients undergoing mastectomy for breast cancer



J.A. Morantes Acevedo^{a,*}, J.C. Álvarez Vega^b, J. Sánchez Vergara^c

^a Resident Anaesthesiologist, Hospital General de México "Dr Eduardo Liceaga", Mexico City, Mexico

^b Anaesthesiologist, Oncology Department, Hospital General de México "Dr Eduardo Liceaga", Mexico City, Mexico

^c Anaesthesiologist/Pain management specialist/Intensive care specialist, Oncology Department, Hospital General de México "Dr Eduardo Liceaga", Mexico City, Mexico

Received 31 October 2016; accepted 1 February 2017

Available online 28 February 2017

KEYWORDS

Pravastatin;
Breast cancer;
C-reactive protein;
Neutrophil/lymphocyte
ratio

Abstract

Introduction: In Mexico, breast cancer is the leading cause of death from malignant tumours in women over 25 years of age. Cancer patients present pro-inflammatory status which, added to the inflammatory response to surgery, worsens their prognosis, not only from a cardiovascular perspective but also by increasing the risk of tumour relapse and the onset of metastases. The objective of this study is to determine the role of pravastatin in the modulation of the systemic inflammatory response to surgical trauma by measuring C-reactive protein (CRP) levels and the neutrophil/lymphocyte ratio (NLR) in breast cancer patients undergoing radical mastectomy.

Methods: Randomised, single-blind, prospective clinical trial in breast cancer patients undergoing mastectomy, divided into two groups of 15 patients each. One of the groups was administered a pre-operative dose of pravastatin 20 mg and the other was not and the pre- and post-surgical inflammatory biomarker levels were measured. The numerical variables are expressed as means and with standard deviation. The comparison between groups was performed with Student's *T*-test.

Results: A total of 30 patients subject to radical mastectomy were enrolled in the study and divided into 2 groups. The mean age was 56.9 years in the control group and 53.4 years in the pravastatin group. It was found that the patients who received a 20 mg pre-op dose of pravastatin presented less CRP elevation, with a mean of 12.6 95% CI (8.34–16.9) vs 43.8 95% CI

* Corresponding author. Dr. Balmis 148, Cuauhtémoc, Col. Doctores, C.P. 06726 Mexico City, Mexico.
E-mail address: jeniffermts15@mail.com (J.A. Morantes Acevedo).

PALABRAS CLAVE

Pravastatina;
Cancer de mama;
Proteína C reactiva;
Índice
neutrófilo/linfocito

(34.3–53.37) in the control group, p 0.0000. Although the changes in the neutrophil/lymphocyte ratio were not statistically significant, p 0.2337, it was less elevated in the pravastatin group, with a mean of 3.57 95% CI (2.02–5.11) vs 7.17 95% CI (3–17.42) in the control group.

Conclusions: The pre-surgical administration of a single dose of pravastatin 20 mg significantly reduced inflammatory biomarker elevation, especially C-reactive protein, making it the ideal drug for routine use in patients undergoing radical mastectomy.

© 2017 Sociedad Médica del Hospital General de México. Published by Masson Doyma México S.A. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Efecto de una dosis única de pravastatina preoperatoria sobre los niveles de proteína C reactiva e índice neutrófilo/linfocito en pacientes sometidas a mastectomía por cáncer de mama

Resumen

Introducción: El cáncer de mama en México ocupa el primer lugar en mortalidad por tumor maligno en mujeres mayores de 25 años. Las pacientes con neoplasias se encuentran en un estado proinflamatorio que sumado a la respuesta inflamatoria generada por el acto quirúrgico como parte su tratamiento empeora su pronóstico no solo a nivel cardiovascular, si no aumentando el riesgo de recidivas tumorales y la aparición de metástasis. El objetivo de este estudio es determinar el papel de la pravastatina en la modulación de la respuesta inflamatoria sistémica que es ocasionada por el trauma quirúrgico mediante la medición de los niveles de proteína C reactiva (PCR) y el índice neutrófilo/linfocito (INL) en pacientes con cáncer de mama sometidas a mastectomía radical.

Métodos: Ensayo clínico prospectivo aleatorizado simple ciego en pacientes con cáncer de mama sometidas a mastectomía divididas en dos grupos de 15 paciente cada uno. A uno de los grupos se les administro una dosis de pravastatina 20mg preoperatoria y al otro no y se midieron los biomarcadores inflamatorios pre y posoperatorios. Las variables numéricas fueron expresadas como medias y con desviación estándar. La comparación entre grupos se realizó mediante T student.

Resultados: Un total de 30 pacientes sometidas a mastectomía radical fueron incluidas en el estudio y fueron divididas en 2 grupos. La media de edad para el grupo control fue de 56.9 años y del grupo de pravastatina 53.4 años. Se encontró que las pacientes que recibieron una dosis de pravastatina preoperatoria 20mg tuvieron menor elevación de la PCR con una media de 12.6 IC95% (8.34-16.9) vs 43.8 IC 95% (34.3-53.37) del grupo control con una p 0.0000 y que los cambios del índice neutrófilo linfocito aunque no fueron estadísticamente significativos con una p 0.2337 tuvieron menores elevaciones en el grupo de la pravastatina con una media de 3.57 IC 95% (2.02-5.11) vs 7.17 IC 95% (3-17.42) del grupo control.

Conclusiones: La administración preoperatoria de pravastatina 20mg única dosis redujo de manera significativa la elevación de biomarcadores inflamatorios especialmente la proteína C reactiva haciéndolo un fármaco idóneo para el empleo rutinario en pacientes a quienes se les realizara mastectomía radical.

© 2017 Sociedad Médica del Hospital General de México. Publicado por Masson Doyma México S.A. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

In Mexico, breast cancer is the leading cause of death from malignant tumour in women over 25 years of age, as up to 52% are diagnosed in late stages. Surgical resection of the primary tumour is essential for oncological control, yet radical mastectomy is reserved for patients in advanced stages.¹

The surgical procedure involves the development of an inflammatory response, which induces mastocyte degranulation and direct activation of the complement, leading to the release/activation of inflammation mediators such as

interleukins and tumour necrosis factor. It has also been suggested that surgical trauma speeds up the development of pre-existing micro-metastases and promotes new metastases.²

In the last ten years, it has been shown that a high systemic inflammatory response is associated to a poor prognosis, irrespective of tumour stage. In particular, white cell counts such as lymphocytes, neutrophils, acute phase proteins such as C-reactive protein (CRP) and albumin have been reported as studies of great prognostic value.³

The role of statins in reducing inflammatory response has been studied in the last few years regarding the different pleiotropic mechanisms that confer stability to the endothelial and vascular functions and oxidative stress,⁴ as well as the direct role found in reducing CRP and neutrophil/lymphocyte ratio levels (NLR), both of which are classified as inflammation biomarkers.⁵ A randomised clinical study conducted by Albert-Ridker et al.⁶ in 2001 showed modulation of inflammatory response with statins, together with reduced tumour stage and greater long-term survival.⁷

The neutrophil/lymphocyte ratio, defined as absolute neutrophil count divided by lymphocyte count, is an effective inflammation marker that is increasingly used to assess results in surgical patients. Its use has been widely shown in critical patients and some cancers. Walsh et al.,⁸ studied the prognostic value of NLR >5 in patients with colorectal cancer and identified it as a prognostic marker. Halazun⁹ showed that a high NLR was a predictor of recurrence and worse survival in oncological patients. Both publications established a cut-off value of 5 for the NLR. The association between a high NLR and poor oncological outcomes is not fully understood. Neutrophils are believed to be a primary source of endothelial growth, which is thought to play a fundamental role in angiogenesis, a process that increases a tumour's ability to spread. Immune response to tumours is determined by cell immunity, which depends on the lymphocyte population. Relative lymphocytopenia could therefore affect prognosis.¹⁰

The objective of this study is to determine the role of pravastatin in the mediation of systemic inflammatory response caused by surgical trauma by measuring CRP levels and the neutrophil/lymphocyte ratio in breast cancer patients undergoing radical mastectomy.

Methods

Single-blind, randomised, prospective clinical trial. This was conducted in the Oncology Department, Hospital General de México "Dr Eduardo Liceaga", from July to December 2015. The protocol was approved by independent ethics committee. 30 breast cancer patients undergoing radical mastectomy were randomised by a simple randomisation table to two groups of 15 patients each. The procedure was explained and informed consent was obtained. 20 mg of pravastatin was administered prior to surgery to group 1 and not to group 2.

The only inclusion criterion was breast cancer patients scheduled for radical mastectomy, irrespective of clinical stage. Patients with concomitant chronic degenerative conditions, such as hypertension and diabetes mellitus, were excluded; patients who were administered doses of peridural local anaesthetic, IV lidocaine in perfusion or NSAIDs in the peri-operative period were eliminated. The patients assigned to group 1 received 20 mg of pravastatin orally from 7 p.m. to 8 p.m. on the evening before the procedure. Pre-operative samples were taken from both groups for CRP and haematic biometry to calculate the NLR in the pre-op room, and they were subject to control 24 h after the surgical procedure.

All the patients received combined anaesthesia and non-invasive monitoring with electrocardiography, non-invasive

blood pressure, pulse oximeter. Pre-anaesthetic medication was administered, Midazolam 30 µg/kg. Epidural blockage from t5 to t8 was applied, depending on the patient's anatomical characteristics, with use of cephalic catheter, not to administer anaesthesia but to verify patency for post-surgical use; basal narcosis Sufentanil 0.5 mcg/kg as inducer propofol (2 mg/kg), muscle relaxant Succinylcholine (1 mg/kg); maintenance was with sufentanil perfusion (0.0002–0.0008 mcg/kg/min), desflurane at 1.0 CAM;

Trans-operative medication: ranitidine 50 mg IV, tramadol 100 mg IV, ondansetron 8 mg.

Statistical analysis

The numerical variables are expressed as means and with standard deviation. The comparison between groups was performed with Student's *T*-test. A *P* value of <0.05 was considered significant. A 95% confidence interval was used. The data analysis was performed by research advisors from Hospital General de México with SAS software.

Results

A total of 30 patients were randomised and distributed in 2 groups. Group 1 received 20 mg pravastatin on the evening prior to the surgery and group 2 was the control group. The mean age was 56.9 years in the control group and 53.4 years in the pravastatin group. Pre-operative paraclinical analyses showed a mean baseline CRP of 4.12 mg/dl (SD 2.45) in the control group vs 2.41 mg/dl (SD 1.22) in the pravastatin group, and the mean baseline NLR was 2.17 (SD 2.22) vs 3.14 (SD 1.15). There were no statistically significant differences between the two groups in the pre-operative period.

When analysed 24 h after surgery, we found that group 1, which had received pravastatin, presented less CRP elevation, with a mean value of 12.6 mg/dl 95% CI (8.34–16.9) SD 7.73 vs 43.8 in the control group, 95% CI (34.3–53.3) SD 17.22 and a *p*-value of 0.0000.

There were no statistically significant differences in post-operative NLR levels between the two groups, *p*-value 0.2337, mean 3.57 95% CI (2.02–5.11) SD 2.78 vs 7.17 95% CI (3–17.42) SD 18.41.

Discussion

Inflammation plays an important role in the physiopathology of cancer, as it could promote carcinogenesis, differentiation and growth of the primary tumour as well as inhibiting apoptosis and increasing the mitotic rate¹⁰; all these factors could make a local or systemic relapse more likely.¹¹ In the last ten years it has been shown that high systemic inflammatory response is associated to poor prognosis, irrespective of tumour stage, in particular white cell count (lymphocytes, neutrophils); acute phase proteins such as C-reactive protein and albumin have been reported as studies of great prognostic value.³

Furthermore, in animal models, the role of pro-inflammatory cytokines has been described in the production of a large variety of symptoms in cancer patients, such as weight loss, depression, fatigue and others.³ It has also been suggested that surgery accelerates the

development of pre-existing micrometastasis and promotes new metastases.¹² The proposed mechanisms include post-surgical suppression of cell immunity. It is known that the manipulation of tumour tissue can spread tumour cells through lymphatic circulation and that the increase in growth factors after surgery and tissue damage promote the development of metastases and onset of new tumour cells.¹¹

The role of statins in reducing inflammatory response has been studied, showing pleiotropic effects and involvement in T-cell regulation, improving immune tolerance, the maintenance and resolution of inflammation and prevention of autoimmune tissue damage.¹³ A direct effect has also been found on the reduction in inflammation biomarkers, which could be markers of tumour recurrence.¹⁴

In 2000, the CARE study¹⁵ followed up patients for 5 years and showed that pravastatin reduced CRP independently from LDL. These data were similar with lovastatin and simvastatin, giving an initial idea of the anti-inflammatory effects of statins. This was, however, a retrospective study. Later, the PRINCE study⁶ (the pravastatin CPR evaluation), a double-blind, randomised, cohort study, administered 40 mg of pravastatin vs placebo in healthy subjects with no history of cardiovascular risk and also measured response to pravastatin in patients with a history of myocardial infarction, showing reductions of up to 14.2% in CRP after 12 and 14 weeks of follow-up with the use of pravastatin, changes that were not found in the placebo group.¹⁶ This study suggested that statins significantly reduce CRP, independent from LDL, which is consistent with the findings of our study, with significant results in modulation of inflammatory response measured with biomarkers.

The statistical analysis shows how the administration of a single pre-operative 20 mg dose of pravastatin, administered uniformly the evening before surgery, significantly reduced elevation of C-reactive protein, with a *p*-value of <0.000 and a mean value of 12.6 vs 43.8 with 95% CI (8.34–16.9).

On the other hand, determination of the neutrophil/lymphocyte ratio shows lower values in the pravastatin than in the control group, but there were no statistically significant differences, with a *p*-value of <0.233 and a mean value of 3.5 vs 7.17 95% CI (2.02–5.11)

We find serious limitations in patient follow-up as they were discharged on the day following the surgery, as well administration the fact that there was no post-operative anaesthetic control.

Conclusions

The pre-operative administration of a single dose of 20 mg pravastatin significantly reduced inflammatory biomarker elevation, especially C-reactive protein, making it a drug that could be routinely used in patients undergoing radical mastectomy.

Studies are required to measure its efficacy in other procedures, although it can be inferred that it is a safe drug with few undesirable effects and readily available, so it could be useful in other fields. Nonetheless, studies are required to validate its use in other scenarios.

Research should be conducted with a larger population, evaluating more specific biomarkers, in order to confirm the drug's utility in inflammatory response modulation in

this and other surgeries. However, as it is an inexpensive drug, administered orally, its pre-operative administration in breast cancer patients could be protocolised in order to improve prognosis and reduce the risk of tumour recurrence.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Funding

The authors received no funding for this study.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

Thanks to the Oncology Department, Hospital General de México "Dr. Eduardo Liceaga" for the collaboration received during the conduct of this study.

References

1. Cardenas J, Bargallo E, Erazo A. Consenso mexicano sobre diagnóstico y tratamiento del cáncer mamario. Quinta revisión Colima. 2013.
2. Gottschalk A, Sharma S, Ford J, et al. The role of the perioperative period in recurrence after cancer surgery. *Anesth Analg*. 2010;110:1636–42.
3. Roxburgh CSD, McMillan DC. Cancer and systemic inflammation. Treat the tumor and treat the host. *Br J Cancer*. 2014;110:1409–12.
4. KONES R. Rosuvastatin, inflammation, C reactive protein, JUPITER and primary prevention of cardiovascular disease. *Drug Des Dev Ther*. 2010;4:383–413.
5. Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on c reactive protein levels, the pravastatin inflammation/CRP evaluation (PRINCE). A randomized trial and cohort study. *JAMA*. 2001;286:64–70.
6. Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *J Am Med Assoc*. 2001;286:64–70.
7. Forero DA, Gutierrez S. Statins as modulators of regulatory t cell biology. *Hind Publ Mediat Inflamm*. 2013;1:1–10.

8. Walsh SR, Cook EJ, Goulder F, et al. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol*. 2005;91:181–4.
9. Halazun KJ, Aldoori A, Malik HZ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *Eur J Oncol*. 2008;34:55–60.
10. Urrejola G, Bambs C, Espinoza M, et al. Un índice neutrófilo/linfocito elevado se asocia a peor pronóstico en cáncer de colon etapa II resecado. *Revista médica de Chile*. 2013;141:602–8.
11. Bugada D, AlleGri M, Lavand P, et al. Inflammation based scores: a new method for patient targeted strategies and improved perioperative outcome in cancer patients. *Biomed Res Int*. 2014;1:1–11.
12. Goldfarb Y, Ben-Eliyahu S. Surgery as a risk factor for breast cancer recurrence and metastasis: mediating mechanisms and clinical prophylactic approaches. *Breast Dis*. 2006;26: 99–114.
13. López Andrade A, Almazan A, Martin JL, et al. Respuesta inmune en el paciente quirúrgico, influencia de la anestesia y transfusión masiva. *Revista española de anestesiología*. 2000;47:67–80.
14. Davignon J. Pleiotropic effects of pitavastatin. *Br J Clin Pharmacol*. 2011;73:518–35.
15. Plehn JF, Davis BR, Sacks FM, y col, for de CARE investigation. Reduction of stroke incidence after myocardial infarction with pravastatin. The cholesterol and recurrent events (CARE) study. *Circulation*. 1999;99:216–23.
16. Menter D, Ramsauer V, Harrirforoosh S, et al. Differential effects of pravastatin and simvastatin on the growth of tumor cells from different organ sites. *PLOS ONE*. 2011;6:1–13.