Journal of Pain & Relief
ISSN: 2167-0846

Márquez et al., J Pain Relief 2015, 4:6
DOI: 10.4172/2167-0846.1000216

Review Article Open Access

Systemic Review on the Use of Diclofenac/B Complex as an Anti-Inflammatory Treatment with Pain Relief Effect for Patients with Acute Lower Back Pain

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Abstract

Objective: the goal of this paper is to perform a systematic review on the use of diclofenac/B complex indicated for acute low back pain, compared to other available therapies for low back pain.

Material and Methods: The systematic review was performed on the following databases: Medline/Pubmed, Cochrane Library (CENTRAL), EMBASE, Imbiomed,LILACS, Artemisa and Nieto Editores, up until February 14th, 2015. A manual searchwas also performed on Google search. Key words were used under the MeSH terminology (Medical Subject Headings): low back pain, lumbago, diclofenac/vitamin B, non-steroidal anti-inflammatory, diclofenac, ibuprofen, naproxen, treatment. Study: Selection was performed by two investigators experts on the subject, selecting those studies with relevant information for the goal of this review.

Results: We found 261 studies with potential interest. Finally, 2 studies were selected, 1 clinical trial and a systematic review. The systematic review by Roelofs et al. (2011), which was done with Cochrane Collaboration and had as a goal to evaluate the effects of NDAIS´s and COX-2 inhibitors on non-specific low back pain treatment and to evaluate which NSAID´s was the most effective. The other selected study was a clinical trial performed by Mibielli et al. in 2009, a randomized study, double-blinded,with parallel groups, that included patients that received diclofenac and B complex andthe other arm received only diclofenac.

Conclusion: Diclofenac/B complex has a pain relief effect, anti-inflammatory and synergic neuro-regenerative effect, and this efficiency has been evaluated in several clinical studies where the administration of diclofenac plus vitamins B1, B6 and B12 decreases pain quicker, apart from being a safe drug.

Keywords: Systemic review; Diclofenac/B complex; Acute lower back pain

Introduction

Pain is the most frequent cause of medical consults. The International Association for the Study of Pain (Asociación Internacional para el Estudio del Dolor) has defined pain as "a sensitive and emotionally unpleasant experience associated with real or potential tissue damage". Perception of pain depends on a neuronal sensitivity system (pain receptors) and afferent nervous pathways that respond to tissue stimuli on such receptors [1].

Chronic pain is a public health problem. It has been suggested that this health problem affects 25 to 29% of general population worldwide. In Mexico, we lack information on the prevalence of chronic pain; however, the National Institute of Social Security, reports that 5% of diseases attended by first contact physicians, are painful by definition [2].

Nowadays a drug exists that combines the anti-neuritic effect of B complex (vitamins B1, B6 and B12) with the anti-inflammatory effect of diclofenac to achieve pain relief effect useful for neurological and neuropathic diseases [3].

Low back pain can be defined as pain or soreness on the lower back, between the inferior border of the last ribs and the inferior crease of the gluteal area, that frequently has a neuritic component with or without expansion to one or both legs, it may involve ostheomuscular and ligament structures, with or without functional limitations that may complicate a daily life and even cause work absenteeism [4].

Low back pain represents an important public health problem in occidental societies due to its elevated prevalence, high impact, magnitude and socio-economic repercussions; it affects labour age population and generates an increase in resource use and work day losses. It is estimated that 60.7% of adults have an episode of lumbar pain syndrome in their lives [5] and there is evidence that it represents one of the main causes of physical limitations in people under 45 years of age. In Mexico, the National Institute of Social Security (IMSS, by its letters in Spanish) reports that low back pain constitutes the eight causes of family medicine consults, registering a total of 907,552 consults at the first level of medical attention [6].

There are several clinical practice guidelines (CPG) for low back pain, (Table 1) according to the recommendations regarding its treatment, it is suggested the use of acetaminophen as a first line drug and the use of NSAID´s as a second line drug, specifically the use of diclofenac, ibuprofen and naproxen [4,7-11].

Given the importance of this disease, the goal of this paper is to perform a systematic review on the use of the association B complex and diclofenac indicated for acute low back pain, compared to other available therapies for this disease, which are recommended on clinical practice guidelines.

Materials and Methods

To perform a systematic review, the research question for the search of clinical studies was: does the association of B complex and diclofenac [diclofenac 75 mg/B complex (cyanocobalamin 1 mg, thiamine 100

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Received September 23, 2015; **Accepted** November 16, 2015; **Published** November 20, 2015

Citation: Márquez M, Guzman S, Soto H (2015) Systemic Review on the Use of Diclofenac/B Complex as an Anti-Inflammatory Treatment with Pain Relief Effect for Patients with Acute Lower Back Pain. J Pain Relief 4: 216. doi:10.4172/21670846.1000216

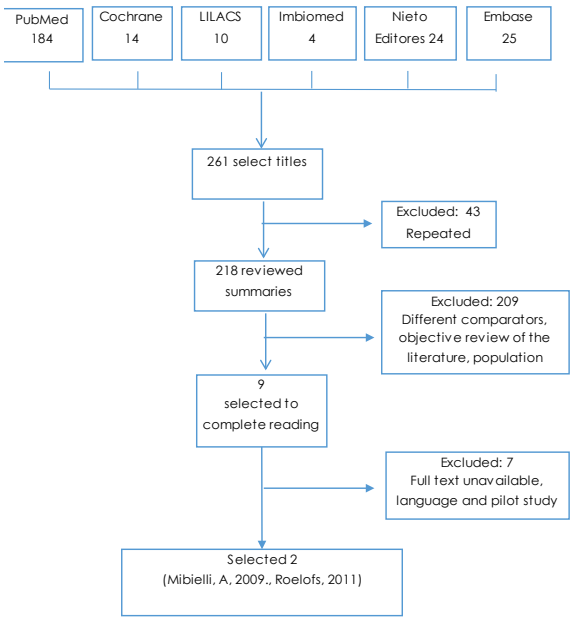

Figure 1: Prisma Alghoritm

mg y pyridoxine 100 mg)] is better for pain relief in patients with acute lower pain than other non-steroid anti-inflammatory agents (specifically ibuprofen, diclofenac and naproxen) as a monotherapy?

Research strategy

Study search was performed on the following databases: Medline/Pubmed, Cochrane Library (CENTRAL), EMBASE, Imbiomed, LILACS, Artemisa and Nieto Editores, up until February 14th, 2015. A manual search was also performed on Google search. Key words were used under the MeSH terminology (Medical Subject Headings): low back pain, lumbago, diclofenac/vitamin b, non-steroidal anti-inflammatory, diclofenac, ibuprofen, naproxen, treatment. Language filters were used (English and Spanish), clinical trials, meta-analysis and systematic reviews, as long as they were adequate to use on our database.

Study Selection

Study selection was performed by two investigators experts on the subject, selecting those studies with relevant information for the goal of this review; clinical studies, systematic reviews and/or meta-analysis were selected, which evaluated the comparison to monotherapy for acute low back pain. The selection only included studies with complete texts, excluding editorial letters and publication abstracts, as well as those with chronic low back pain, patients that received other additional medications different from those relevant to this study and those performed in children. Discrepancies were resolved by mutual discussion. The agreement between the two reviewers for selection and validity assessment of trials was scored by kappa coefficient.

Data extraction from individual studies

The context of all selected studies was obtained on an initial database with the goal of deciding if the obtained data was comparable or not, for a possible meta-analysis.

Quality of the studies evaluation

In the selected studies, the complete text was searched to ensure that it fulfilled the required information from the clinical studies by the Consolidated Standards of Reporting Trial from 2010 and by the PRISMA Declaration for the systematic reviews and meta-analysis [12].

Clinical Practice Guidelines	Recommendation
Diagnostic, treatment and prevention of acute and chronic lower back pain at the first lever of Attention. Cenetec, 2009.	First line: acetaminophen Second line: NSAID's (diclofenac, naproxen, sulindac) during short periods of time with the lowest possible dose, as long as there is no contraindication (There is no evidence that there is a difference in pain relief efficiency amongst different NSAID's).
Clinical Practice Guidelines on Llower back pain. Sanitation Department of the Spanish Government, 2007.	First Line: acetaminophen Second line: NSAID's (ibuprofen, diclofenac and naproxen), any NSAID´s is equally efficient in lower back pain treatment).
Guideline for the Low Back Pain. Institute of Health Economics, 2011	Acute and Chronic lower back pain: First line: acetaminophen Second line: NSAID's (ibuprofen and diclofenac), no NSAID's is more efficient to the other.
Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society	First line: acetaminophen and NSAID's
Guideline for the evidence-informed primary care management of low back pain	First line: acetaminophen Second line: NSAID's
Clinical Practice Guidelines for non-specific lower back pain. Spanish Work Team for the European Programme COST B13, 2005	According to the intensity of the pain, the recommendations are: Acetaminophen Normed NSAID's (not "over the counter") NSAID's (normed) plus muscle relaxants during less than a week.

Source: [4,7,8,10,11,25].

Table 1: Clinical practice national and international guidelines for lower back pain treatment.

Results

Study selection

With the search algorithm (Table 1), we found 261 studies with potential interest. After eliminating repeated studies and after reading all abstracts, it was decided to review a total of 9 texts, which were analysed for their subsequent evaluation. Finally, 2 studies were selected, 1 clinical trial and 1 systematic review. Agreement between two reviewers for study selection was 0.87 and the kappa value shown concordance important.

Study characteristics

The systematic review by Roelofs et al. from 2011 [13], which was done by Cochrane Collaboration and had as a goal to evaluate the effects of NDAIS´s and COX-2 inhibitors (meloxicam 7.5/day and 15 mg/day, valdecoxib 40mg/day, etoricoxib 60 mg/day) on non-specific low back pain treatment and to evaluate which NSAID´s was the most effective; patients over 18 years of age were evaluated that required pain treatment that was caused by non-specific low back pain with or without sciatic pain. They included 65 clinical trials with a total of 11,327 patients (Tables 2-4).

The other selected study was a clinical trial performed by Mibielli et al. in 2009 [14], a randomized study, double-blinded, with parallel groups, that included 187 patients that received diclofenac (50 mg) and B complex (thiamine, pyridoxine and cyanocobalamin [50 mg/50 mg/1 mg] twice a day and 185 patients that received diclofenac 50mg twice a day.

1.	Low Back Pain [MeSH Terms]
2.	Lumbago [MeSH Terms]
3.	Diclofenac/vitamin b [All Fields]
4.	Diclofenac [All Fields]
5.	Non-steroidal antiinflammatory [All Fields]
6.	Ibuprofen [All Fields]
7.	Naproxen [All Fields]
8.	(1 OR 2) AND (3 OR 4 OR 5 OR 6 OR 7)
9.	Treatment [MeSH Terms]
10.	8 AND 9
11.	systematic[sb]
12.	Meta-Analysis[ptyp]
13.	Clinical Trial, [ptyp]
14.	Clinical Trial, Phase IV[ptyp]
15.	Clinical Trial, Phase III[ptyp])
16.	Humans [MeSH Terms]
17.	10 AND (11 OR 12 OR 13 OR 14 OR 15) AND 16

Table 2: Search algorithm used in different databases.

Author	Efficiency methods	Adverse effects	Conclusions
Mibielli, et al. [14]	With a total follow up period of 7 days, and after a 3 day treatment evaluation, 46.5% of patients within the diclofenac/B complex group ended the study with success due to treatment versus 29% of patients that ended the study within the diclofenac group (p=0.005)	There were no statistical differences on safety between both study groups.	The combination of diclofenac/B complex was superior to diclofenac monotherapy for lower back pain relief after 3 days of treatment. As an inconvenience to this study, VALS measurements were only taken before the subject left the study, after 3, 5, or 7 days.

Table 3: Description of the selected clinical trial.

Author	Efficiency methods	Adverse effects	Conclusions
Roelof et al. [13]	There is moderate evidence that NSAID's are more effective than acetaminophen to acute lower back pain, but acetaminophen has less adverse effects. There is strong evidence that the different NSAID's, including COX-2 inhibitors are equally effective for acute lower back pain.	COX-2 inhibitors have few side effects compared to traditional NSAID's and the difference was statistically significant.	The evidence of 65 studies included suggests that NSAID's are effective for short tern pain relief and chronic one without cyatic pain. Nevertheless the effect is small and not clear if any NSAIDs is more effective than other one.

Table 4: Description of the selected systematic review.

Quality of the studies

Regarding the systematic review performed by Roelofs et al, it fulfilled all the suggested items by the PRISMA Declaration, and it's worth mentioning that because it is a document from the Cochrane Collaboration, whose strict method is the most adequate. The clinical trial elaborated by Mibielli, according to the CONSORT items, the title was not identified as a clinical trial, and the study registry name was not specified, while the other items are all described within the document. For these reason we can conclude that both studies have adequate quality.

Discussion

For treatment of low back pain, NSAID's are the most prescribed drugs worldwide. NSAID's are mildly effective for short term treatment in patients with low back pain, both acute and chronic, however they are more effective than drugs such as acetaminophen, opioids or muscle relaxants, and comparing NSAID's with the new COX-2 inhibitors, these last ones are equally effective but are associated with less adverse effects, particularly gastric ulcer and renal damage [13].

Several studies have reported that thiamine, pyridoxine and cyanocobalamin have an important role for the adequate function of the central nervous system, the myelin cover and other cell structures, it is essential for nutrition, axonal transport, neural excitability and neurotransmitter synthesis, and combined with diclofenac they present a synergic action in ostheomuscular diseases and pain management [3,15,16]. The mechanisms are currently unknown, it has been proposed that the antihyperalgesic mechanisms of B vitamins include its ability to increase afferent inhibitory control of nociceptive neurons at the spinal cord [17], to improve sensory nerve conduction velocity [18] and to reduce neuronal hyperexcitability by altering sodium currents in injured dorsal root ganglia [19]. Moreover, the individual administration of thiamine and pyridoxine produce antinociception in acetic acid-induced pain or pain induced by supramaximal electrical stimulation of afferent C fibers, in the last years it has been postulated that B vitamins induced antinociception could result from activation of opioid receptors or nitric oxide release [20].

The indication of low back pain in the association diclofenac/B complex obeys the clinical effects that have been reported from the pain relief effect related to the synthesis and metabolism of neurotransmitters such as acetylcholine, gamma-aminobutyric acid, dopamine and serotonin, that participate in their liberation from the pre-synaptic membrane, as well as the synthesis of sphingolipids that constitute the myelin cover, which translates into a pain relief effect [3], these studies are experimental in pre-clinic phase but evaluate different kind of pain, not specifically low back pain [17,18,20-22]. Respect to low back pain, a double-blind randomised, placebo-controlled study clinical study that examine the efficacy and safety intramuscular vitamin B12, showed a statistically significant difference in favour of the active treatment both for visual analogic scale (VAS) and Disability Questionnaire (DQ) and decreasing the consumption of paracetamol [23]. Another clinical trial that studied combination of B vitamins and diclofenac was performed by Kunt et al., studying 53 patients with acute low back pain reporting good or excellent results in pain management in 77.4% and moderate effects in 15.1% [24], however the language of this study is Germany by this reason not is included in this paper.

It is worth mentioning that there are several published studies that could not be included in this systematic review given that even though they study patients with low back pain, it was not possible to obtain the complete version of such studies and they are in different languages to Spanish or English. However the evaluated results indicate an improvement in pain with a combination of diclofenac with thiamine, pyridoxine and cyanocobalamin, such studies are described here: Vetter et al, evaluated 256 patients with low back pain comparing diclofenac versus diclofenac with vitamin B1, B6 and B12, to determine if the duration of treatment was shortened with the addition of B complex, and all the results were evaluated with the Hoppe Pain Questionnaire (HPQ) (this questionnaire evaluate different aspects of the perceived pain on a 7 point Likert scale, comprises 4 primary scales: pain suffering, pain anxiety, pain sharpness and pain rhythm) [25]; and showed superiority of diclofenac with vitamin B1, B6 and B12; they documented adverse effects in 39 patients, 14 of which required to stop treatment [26]. Also Bruggemann et al studied in 418 patients the clinical efficiency of diclofenac with B complex for a maximum

period of 3 week compared to diclofenac. The evaluation from the HPQ and other additional data related to pain intensity indicated better results with the combination therapy; regarding safety there was no statistically significant difference between both groups [27]. However, given the perception of clinical practice and published work [28,29] it looks like the response to NSAID's varies amongst individuals, which makes indication and evaluation of response to these drugs to be individualized, and thus the selection of the drugs will depend fundamentally on the patients characteristics, the NSAID's profile and the physician experience with their use [30].

Although the previously described studies have showed beneficial effects of using diclofenac/B complex, we notice that there are very few published studies that evaluate it for low back pain, a chronic disease that affects patient's life quality and that the probability for general-population to suffer it is high.

Apart from these studies, the combination of diclofenac with thiamine, pyridoxine and cyanocobalamin was also evaluated in patients with fractures or surgeries of the lower extremities. The first study was a pilot clinical trial where the combination B complex with diclofenac was evaluated; the pain was evaluated with a visual analogue scale that showed a significant decrease at 12, 24, 36 and 48 hours post-surgery, and in general drugs were well tolerated [31]. The second study was performed by Ponce et al., and it evaluated the combination of diclofenac and B complex in 122 patients with acute lower pain from a fracture or surgery of lower extremities showing a significant decrease of pain compared to diclofenac, which means that adding B complex increases pain relief effect of diclofenac [32].

This favourable evidence of the use of diclofenac/B complex could indicate that given the beneficial results of its use in the population, it could be feasible to search for a better clinical scenario to be able to use, and thus be able to evaluate the effects of diclofenac/B complex in different pain scenarios for which it may be indicated.

For the studies selected from this systematic review, in the paper performed by Roelofs et al. included the trials performed by Vetter and Bruggemann (previously described). However, considering the sample size of patients treated in both studies, regarding the total sample from all studies, they weren't able to find statistically significant differences for the combination of diclofenac and vitamins B1, B6 and B12.

Respect to the study by Mibielli et al, corroborates the mayor pain relief effect of diclofenac while combined with thiamine, pyridoxine and cyanocobalamin.

In this work we also reviewed the CPG for other therapeutic indications of diclofenac/B complex, however only the general use of NSAID's is recommended in certain diseases such as neck pain or arm pain; in cases of neuropathies the use of NSAID's associated with tricyclic antidepressants, and for fibromyalgia the use of NSAID's associated to other drugs. However, none of the CPG suggests the use of diclofenac/B complex, and we could neither find clinical studies that evaluate the indications we previously mentioned. For alcoholic neuropathies only the use of Vitamin B is recommended, but not diclofenac; for radiculitis physical therapy is recommended, and for carpel tunnel syndrome the treatment is surgery.

Conclusion

We can conclude that diclofenac/B complex has a pain relief effect, anti-inflammatory and synergic neuro-regenerative effect, and this efficiency has been evaluated in several clinical studies where the administration of diclofenac plus vitamins B1, B6 and B12 decreases pain quicker, apart from being a safe drug. Nevertheless, the evidence in literature that seem to favour the use of diclofenac/B complex is slim and does not fulfil with the adequate quality regarding the obtained benefits in patients that use it for the approved indications. We suggest increasing scientific data to conclude more on the use of diclofenac/B complex for low back pain.

Declaration of Interests

The authors declare no competing interest, but this study was funded by Merck Serono.

References

1. Puebla F (2005) Tipos de dolor y escala terapéutica de la O.M.S. Dolor iatrogénico. Oncología 28: 139-143.
2. Covarrubias A, Guevara U, Gutiérrez C, Betancourt J, Córdova J (2010) Epidemiología del dolor crónico en México. Revista Mexicana Anestesiología 33: 207-213.
3. Merck (2011) Información para prescribir amplia Dolo-Neurobion.
4. Secretaría de Salud (2009) Diagnóstico, Tratamiento y Prevención de Lumbalgia Aguda y Crónica en el primer nibel de atención. México.
5. van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, et al. (2006) Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. Eur Spine J 15 Suppl 2: S169-191.
6. División Técnica de Información Estadística en Salud (DTIES) (2007) Motivos de Demanda de Consulta Externa. Unidad de Investigación, Educación y Políticas de Salud. División de Prestaciones.
7. Irazusta P, Alcorta M y Aguirre L (2007) Guía de prática clínica sobre lumbalgia . España: Departamento de sanidad del Gobierno de Vasco.
8. Institute of Health Economics (2011) Guideline for the Low Back Pain. Canada: IHE.
9. Chou R, Qaseem A, Snow V, Casey D, Cross T, et al. (2007) Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society., Annals of Internal Medicine147: 478-491.
10. Agency for Healthcare Research and Quality (2011) Guideline for the evidence-informed primary care management of low back pain. National Guideline Cl.
11. Grupo Español de Trabajo del Programa Europeo COST B13 (2005) Guía de Práctica Clínica Lumbalgia Inespecífica. España: European Comission.
12. Schulz, K. Retrieved. Retrieved. [En línea] 26 de 09 de 2013.
13. Roelof P, Deyo R, Koes B, Scholten R, Van Tulder M (2011 Non-steroidal anti-inflammatory drugs for low back pain (Review). The Cochrane Collaboration 2: 1-82.
14. Mibielli MA, Geller M, Cohen JC, Goldberg SG, Cohen MT, et al. (2009) Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: the DOLOR study. Curr Med Res Opin 25: 2589-2599.
15. Rizzo JF 3rd1 (1995) Adenosine triphosphate deficiency: a genre of optic neuropathy. Neurology 45: 11-16.
16. Meador KJ, Nichols ME, Franke P, Durkin MW, Oberzan RL (1993) Evidence for a central cholinergic effect of high-dose thiamine. Ann Neurol 34: 724-726.
17. Fu QG, Carstens E, Stelzer B, Zimmermann M (1988) B vitamins suppress spinal dorsal horn nociceptive neurons in the cat. Neurosci Lett 95: 192-197.
18. Jolivalt CG, Mizisin LM, Nelson A, Cunha JM, Ramos KM, et al. (2009) B vitamins alleviate indices of neuropathic pain in diabetic rats. Eur J Pharmacol 612: 41-47.
19. Song X, Huang Z y Song X (2009) Thiamine suppresses thermal hyperalgesia inhibits hyperexcitability, and lessens alterations of sodium currents in injured dorsal root ganglion neurons in rats. Anesthesiology 110: 387-400.
20. Reyes G, Medina R, Flores F (2006) Analgesic effects of B vitamins: a review. Curr Top Pharmacol 10: 1-31.
21. Rocha-González HI, Terán-Rosales F, Reyes-García G, Medina-Santillán R, Granados-Soto V (2004) B vitamins increase the analgesic effect of diclofenac in the rat. Proc West Pharmacol Soc 47: 84-87.

22. Yu C, Liu Y, Liu S, Yan M, Hu S, Song X. (2014) Systematic administration of B vitamins attenuates neuropathic hyperalgesia and reduces spinal neuronal injury following temporary spinal cord ischaemia in rats. Pain 114: 266-77.

23. Mauro GL, Martorana U, Cataldo P, Brancato G, Letizia G (2000) Vitamin B12 in low back pain: a randomised, double-blind, placebo-controlled study. Eur Rev Med Pharmacol Sci 4: 53-58.

24. Kunt T (1978) [Complaints in the lumbosacral region and their management with Dolo-Neurobion]. Fortschr Med 96: 299-300.

25. Hoppe F Hamburger Schmerz-Adjektiv-Liste (HSAL). Weinheim.

26. Vetter G, Bruggemann G, Lettko M, Schwieger G, Asbach H, et al. (1988) Shortening diclofenac therapy by B vitamins. Results of a randomized double-blind study, diclofenac 50 mg versus diclofenac 50 mg plus B vitamins, in painful spinal diseases with degenerative changes. Zeitschrift fur Reumatologie 47: 351-62.

27. Brüggemann G, Koehler CO, Koch EM (1990) [Results of a double-blind study of diclofenac + vitamin B, B6, B12 versus diclofenac in patients with acute pain of the lumbar vertebrae. A multicenter study]. Klin Wochenschr 68: 116-120.

28. Pincus T, Callahan LF (1993) Variability in individual responses of 532 patients with rheumatoid arthritis to first-line and second-line drugs. Agents Actions Suppl 44: 67-75.

29. Bori Segura G, Hernández Cruz B, Gobbo M, Lanas Arbeloa A, Salazar Páramo M, et al. (2009) [Appropriate use of non-steroidal anti-inflammatory drugs in rheumatology: guidelines from the Spanish Society of Rheumatology and the Mexican College of Rheumatology]. Reumatol Clin 5: 3-12.

30. Loza E (2011) AINEs en la práctica clínica: lo que hay que saber. Sist Nac Sal 35: 88-95.

31. Garza A, Monroy R, Soto M, Reyes G, Carillo L, et al. (2008) A pilot study of the effect of diclofenac with B vitamins for the treatment of acute pain following lower-limb fracture and surgery. Proceedings of the Western Pharmacology Society 51: 70-2.

32. Ponce H, Ortiz I, Garza F, Monro R, Soto M, et al. (2012) Effect of diclofenac with B vitamins on the treatment of acute pain originated by lower-limb fracture and surgery. Pain research and treatment 2012: 1-5.