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Review Article

Interaction between anti-hypertensive and non-steroidal anti inflammatory drugs: implications in management of osteoarthritis and opinion on a compromise therapy

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ABSTRACT: The premise for this article is that a significant proportion of patients presenting in the clinic with osteoarthritis have hypertension as co-morbidity. A common drug of choice in managing symptoms of osteoarthritis including those affecting the knee joint is the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) groups. It has been reported however that NSAIDs diminish the effects of anti-hypertensive drugs and may lead to an ineffective hypertension therapy. In order to avoid complications in the health of the patient with concomitant hypertension and osteoarthritis and who are on both antihypertensive and NSAIDs, it becomes imperative to consider using non-pharmacologic approaches such as physiotherapy in managing the symptoms of osteoarthritis in this group of patients and thereby maximizing the effects of their antihypertensive therapy. This is more so that information exists on efficacy of physiotherapy in form of therapeutic exercises and electrotherapeutic modalities in management of clinical features of osteoarthritis.

KEY WORDS: NSAIDs; Anti-hypertensive drugs; Interaction; Osteoarthritis; Management

INTRODUCTION

Arthritis is an important cause of pain, disability, economic loss and burden on the individuals and society.¹ Osteoarthritis is the most common form of arthritis and joint disorder worldwide.² It is a chronic degenerative disease of synovial joints with exacerbations of acute symptoms, resulting from degeneration of articular cartilage together with changes in subchondral bone and mild intra-articular inflammation.³

Osteoarthritis typically begins after age 40 years and symptoms begin in middle age, with a progression as age advances.⁴ Its prevalence after the age of 65 years is about 60% in men and 70% in women³ though the prevalence of hip OA is higher in men while the prevalence of knee OA is higher in women.⁵ Osteoarthritis is a leading cause of disability in the society, and represents the most prevalent articular disease in the elderly.⁶ The objective of this review is to highlight the importance of a non-pharmacologic approach (physiotherapy) in management of osteoarthritis among hypertensive patients.

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MANAGEMENT OF OSTEOARTHRITIS

There appears to be no established curative care for osteoarthritis or OA, hence the main goals of treatment are to relieve pain, and

maintain or improve functional status.^{4,7} Treatment of OA is usually tailored to the need of each individual as joints involvement are highly varied, so also are the rate of progression, severity of symptoms, degree of disability and responses to specific forms of treatment.⁸ Pain relief in OA enables patients to regain their mobility and is therefore a key goal in the management.⁹ Therapeutic options in osteoarthritis involve non-pharmacological and pharmacological interventions.

Non--pharmacological interventions

Education and support: A meta-analysis of 10 trials that contrasted patient educations with the therapeutic effects of non-steroidal anti-inflammatory drugs reported a significant beneficial effect of education on joint pain.¹⁰ Behavioural changes such as weight reduction and appropriate dieting are essential for good management of OA.¹¹ Social and emotional support has been shown to produce significant improvement in pain and functional status.¹²

Orthotic devices: Orthotic devices are used to relieve pain and prevent deformities. These may include wedge insole, walking sticks, braces and patella taping.⁸ Bracing can be effective in patients who have relatively focused uni-compartmental medial or lateral osteoarthritis. Thus, valgus bracing is often used for varus knees in which osteoarthritis primarily involves the medial compartment. Less frequently, varus bracing may be indicated for lateral-compartment osteoarthritis associated with a valgus deformity. It has been observed that even when a brace is prescribed and found to be efficacious, many patients stop using it after a short time.¹³

Surgery: Surgical treatment is often reserved for patients who have severe disability or uncontrollable pain.⁴ The type of procedure that is appropriate for an individual OA patient will depend on a variety of patient characteristics that have to be evaluated by an orthopaedic surgeon. These surgical interventions may include arthroplasty (partial or total), arthrodesis, osteoplasty, chondroplasty, and tidal irrigation.¹⁴

Physiotherapy: This is considered to be of immense benefit in treatment of osteoarthritis. It has been suggested that ideally all new patients diagnosed with OA should be seen by a physiotherapist.¹³

The mainstay of physiotherapy in OA management is therapeutic exercises coupled with electrotherapeutic modalities.¹¹

Indications, contra-indications, dosage and precaution are however as important in physiotherapy as they are in drug therapy.⁸ Physiotherapy for osteoarthritis of the knee is aimed at producing decrease in inflammation, maintain or improve range of motion and strengthen muscles, especially the quadriceps. Methods used to treat pain, inflammation, and weakness includes cold and heat therapy, ultrasound, shortwave diathermy, interferential, laser, transcutaneous electrical neuromuscular stimulation, and faradic muscle stimulation.¹³

Therapeutic exercises may decrease pain, increase muscle strength and range of motion, as well as improve endurance and aerobic capacity in OA patients.^{8,15} These exercises may include open and closed kinetic chain exercises. Open kinetic chain exercises are typically non-weight bearing with the movement occurring at the knee joint.⁴

In a study where 61 women with well-defined knee osteoarthritis were alternately assigned to receive diathermy (random assignment to receive ultrasound or short-wave diathermy) alone or diathermy plus exercise, the exercise group showed a significantly greater improvement in the incapacity score compared with the non-exercise control group and also showed greater improvement in measured muscle strength.¹⁶

The use of heat and cold, ultrasound, transcutaneous electrical nerve stimulation (TENS) and interferential are some of the electrotherapeutic approaches to OA management.^{5,8} The Philadelphia Panel evidence-based clinical practice guidelines on selected rehabilitation interventions for knee pain have observed that transcutaneous electrical nerve stimulation (TENS) and therapeutic exercises are beneficial for knee osteoarthritis.

Pharmacological interventions

Pharmacological interventions in the management of OA include:

Simple Analgesics: Simple analgesics such as Acetaminophen are considered as first line oral therapy for symptomatic knee OA with mild pain.¹⁷ Acetaminophen is innocuous and potent. However, acetaminophen is not as efficacious as non-steroidal anti-inflammatory drugs in management of moderate to severe pain of OA.¹⁷

Corticosteroids: Intra-articular corticosteroids are widely used in the management of patients with OA of the knee, most commonly in those

who have appreciable effusion or other signs of active inflammation.¹³ There is a good evidence to support the use of intra-articular corticosteroids in patients with knee osteoarthritis, but because of the potential for multiple intra-articular injections to accelerate cartilage damage, they should not comprise the only treatment of patients with chronic osteoarthritis.¹³

Chondroprotective agents: To date, no measures have been convincingly shown to modify the rate of structural changes in cartilage or subchondral bone, which constitute the underlying disease process. Chondroitin and glucosamine compounds have been proposed as agent that may modify these structures but only their analgesic and anti-inflammatory effects have been established.¹⁸ Chondroitin and glucosamine have become popular as putative symptomatic and disease-modifying therapies for osteoarthritis of the knee. It is hypothesized that these important constituent components of cartilage matrix can be ingested, enter plasma, cross the blood-synovial fluid barrier, and enter synovial fluid in sufficient concentrations to provide analgesia and promote cartilage healing. The mechanisms, if any, underlying these alleged therapeutic effects remain undiscovered. Given their widespread use by patients, it is fortunate that these products appear to be safe, and they can be a useful adjunct, especially in patients who cannot tolerate NSAIDs.¹⁸

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): These are among the most frequently used drugs in many countries to manage OA.¹⁹ Non-steroidal anti-inflammatory drugs are the drugs of choice because their efficacy in management of OA is well proven.¹⁷ Population-based studies in the United States of America have shown that, on any given day, 10-20% of elderly people have a current NSAIDs prescription. Anti-inflammatory drugs may be administered orally, sublingually, intramuscularly, or topically and they are also available in suppository form.

Non-Steroidal Anti Inflammatory Drugs (NSAIDs) work by inhibiting the enzyme cyclo-oxygenase (cox) responsible for prostaglandin synthesis.²⁰ Cyclo-oxygenase (cox) exists in two isoforms, cox-1 and cox-2. Conventional or non-selective NSAIDs do inhibit both cox-1 and cox-2, while cox-2 selective inhibitors inhibit only cox-2.²¹ Cox-1, the constitutive form of the enzyme is expressed through the body and provides certain homeostatic functions such as

maintaining normal gastric mucosa, influencing renal blood flow and enhancing blood clotting by aiding platelet aggregation.²² Cox-2, the inducible form is expressed in response to inflammatory and other physiologic stimuli. Cox-2 is involved in the production of those prostaglandins that give rise to articular pain and swelling during inflammatory process.²²

Inhibition of cox-1 is identified to be the main cause of the gastrointestinal toxicity, which includes heartburn, gastrointestinal ulceration and bleeding.²³ Since the beneficial anti-inflammatory and analgesic effects occur through the inhibition of cox-2, drugs that would inhibit cox-2 while sparing cox-1 have been developed. Despite the gastrointestinal tolerance of cox-2 selective inhibitors, it is established that renal and cardiovascular effects of cox-2 selective inhibitors are similar to those of non-selective NSAIDs.²⁴ These include sodium, potassium and water retention, impaired renal function, hypertension and oedema. These deleterious effects are amplified in patients with cardiovascular disorders such as hypertension.²³ Other complications of traditional NSAID treatment include gastrointestinal bleeding as well as hepatic, renal, and platelet dysfunction. Indeed, information from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) Post-Marketing Surveillance Programme suggests that at least 16,500 deaths per year in the United States are caused by NSAID-induced GI bleeding in arthritis patients.²⁵ This is a cause for great concern considering that arthritis, and especially osteoarthritis, is not generally considered a life-threatening disease.

HYPERTENSION & OSTEOARTHRITIS

Hypertension, the most common cardiovascular disease²⁶ can result in target organ damage,²⁷ cause increased incidence of renal and cardiac failure as well as stroke.²⁶ The age group commonly affected by hypertension is 50 years and above.²⁸ Osteoarthritis and hypertension are thus two common conditions which may co-exist and for which anti-hypertensive drugs and NSAIDs are prescribed.²⁹

Among the elderly, in whom the prescriptions of both NSAIDs and antihypertensive are highest, 12 to 20 million people in the United States are estimated to use both classes of drugs concomitantly.³⁰ In a study of drug utilization pattern among hypertensive patients in a tertiary care setting in South-Western Nigeria, osteoarthritis was found to be the

second highest co-existing disease with hypertension, after diabetes. NSAIDs were reported as being concurrently taken with anti-hypertensive drugs in this group of patients.³¹ The simultaneous use of these two drug classes, along with the multitude of medical problems in the elderly population that decrease drug metabolism or require multiple drug therapy, may predispose these patients to the risk of developing drug-drug or drug-disease interactions.³¹⁻³³ It has been established that NSAIDs do antagonize the anti-hypertensive effects of diuretics, ACE inhibitors and calcium-channel antagonists and beta-blockers.²⁹ Treatment of hypertension may thus be rendered ineffective due to concomitant use of NSAIDs.²⁷

The NSAIDs do have antagonizing effects on anti-hypertensive drugs²⁹ and the concomitant administration of COX-2 inhibitors may destabilize blood pressure control in hypertensive patients treated with anti-hypertensive agents. Treatment of hypertension may thus be found to be ineffective due to concomitant use of NSAIDs.²⁷

The NSAIDs have been reported in randomized controlled trials to elevate blood pressure in:

- some previously normotensive persons with and without antihypertensive therapy,
- patients with untreated mild hypertension or treated with single doses of antihypertensive agents, and
- in hypertensive persons whose blood pressure had been controlled by drug therapy.³⁴⁻³⁶

Non-steroidal anti-inflammatory drugs affect blood pressure via the renin-angiotensin pathway, retention of sodium and water in the kidneys, inhibition of prostaglandin and production of vasoconstrictors.²⁰ According to Hawkey and Langman³³ although NSAIDs affect renal blood flow, their most consistent effect is in enhancing renal sodium reabsorption as a result of cyclo-oxygenase inhibition predisposing to increased blood pressure, peripheral oedema and hyperkalaemia. The NSAIDs may have serious consequences in individuals at risk for cardiovascular disorders since this group of drugs may cause water retention. Hypertension can also be aggravated or the effects of anti-hypertensive drugs countered. Large meta-analyses suggest that NSAIDs treatment elevates blood pressure by an average of 5mmHg.^{32, 34} It is important to note that an overview of randomised trials of anti-hypertensive treatment found that a 5 to 6 mmHg increase in diastolic blood pressure

over a few years might be associated with a 67% increase in total stroke occurrence and a 15% increase in coronary heart disease.³⁷

According to White,³⁸ available information indicate that some NSAIDs and COX-2 inhibitors at high doses might result in increased cardiovascular events in patients who use them compared with nonusers of the NSAIDs, while others might not. This researcher therefore suggested that factors to consider for patient safety include the direct effects of nonselective NSAIDs and of COX-2-selective inhibitors on fluid retention and blood pressure, differences among these agents with regard to associated gastrointestinal adverse event rates and the utility of simultaneous anti-inflammatory therapies with gastroprotective agents such as proton pump inhibitors when patients require cardioprotective doses of aspirin.³⁸

IS THERE A WAY OUT?

Physiotherapy and other non-pharmacological therapies of OA are recommended. Pain relief is a key goal in the management of osteoarthritis and NSAIDs, more often than not, are prescribed.⁹ It may be possible to manage some clinical features of OA such as (specifically) pain; joint stiffness and functional limitation in hypertensive patients with physiotherapy only and thus avoid NSAID - antihypertensive drug-drug interaction. Such practice may help avoid the adverse effects of NSAIDs particularly in patient with cardiovascular disorders.⁸ Physiotherapy has been found to be effective in the management of osteoarthritis generally^{3, 13, 15} irrespective of the blood pressure status of the patients. It may as well be the way out thus the compromise therapy.

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