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EVALUATING THE CARDIOVASCULAR RISKS ASSOCIATED WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) NEW APPROACHES IN PAIN MANAGEMENT

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Abstract

Background: Analgesic anti-inflammatory drugs, especially NSAIDs, are commonly used in treating pain while they bear a range of cardiovascular hazards such as elevated risk of myocardial infarction and stroke. Establishing the magnitude of these risks in these subgroups is important in maximizing pain relief approaches while minimizing adverse cardiovascular repercussions.

Objectives: In order to assess the cardiovascular risks of NSAIDs in patients as well as consider other better pain relief strategies that address such risks.

Study design: A prospective cohort study

Duration and place of study. Department of pharmacology Watim Medical and Dental College Rawalpindi from jan 2021 to jan 2022

Methods: This prospective cohort study recruiting 120 patients, aged between 45 and 75 years and on NSAID therapy for chronic pain. Patients were divided into two groups: participants with a history of cardiovascular disease (n= 60) and those participants with no history of cardiovascular disease (n= 60). The cardiovascular events were recorded after three months and then for the next three months. For cardiovascular outcome measures SD was estimated, and p-value was used to evaluate the statistical difference.

Results: Patients with prior cardiovascular disease had increased cardiovascular event risk by 30% ($p<0.05$). The mean incidence of myocardial infraction was 12 % (± 2.5) in the cardiovascular group and 5 % (± 1.8) in the non cardiovascular group. Consumption of topical NSAIDs reduced cardiovascular occurrences of the disease to significance level $p < 0.01$. Milliseconds to hours to days and overall adverse events were fewer with acetaminophen as an alternative.

Conclusions: Patients on NSAID therapy have a three times higher cardiovascular risk than people not on NSAID therapy and patients with preexisting cardiovascular disease have a 5 fold higher risk of suffering from a cardiovascular event. Other OTEs like non oral topical NSAID and Acetaminophen proves less risky, especially among the vulnerable people. The guidelines for the future should focus on the strategies concerning the treatment of pain for each patient.

Keywords: NSAIDs, cardiovascular risks, pain treatment, alternatives

Introduction

NSAIDs are used to address issues of pain, fever and inflammation in conditions like osteoarthritis, rheumatoid arthritis and acute musculoskeletal sprains/strains. They obtain their therapeutic impact mainly through the suppression of cyclooxygenase (COX) enzymes, which are important in prostaglandin formation. Prostaglandins are the hormone like substances playing the role of inflammatory mediators, nociceptive substances being involved in the signaling of pain and substances that maintain GI tract integrity [1]. However, like any other drugs, NSAIDs are not free from side effects, and new research pointed to the fact that their use poses moderate cardiovascular risk, especially for patients with underlying cardiovascular diseases [2]. There are two main forms of COX enzymes: The constitutive isoform, COX-1, is involved in physiological processes including GI mucosal protection, and platelet aggregation and the inducible isoform, COX-2 is up regulated during inflammation [3]. Nonselective drugs COX-1 and COX-2 were developed but with side effects on ulcers in the gastrointestinal tract, selective drugs like celecoxib were developed. Nevertheless, selective COX-2 inhibition has been linked to thrombotic events such as MI and stroke because TXA2 that encourages platelet aggregation is favoured over the vasodilatory PGI2 [4]. These changes make the blood more pro-thrombotic and contributes to the elevation of risk for cardiovascular diseases [5]. Common cardiovascular effects related to NSAIDs depend on the kind of NSAID, the dose, the period of treatment, and the existing pathological conditions of the patient. For instance, diclofenac, and ibuprofen are safety-wise, more dangerous than naproxen when it comes to the cardiovascular issues [6]. In addition, the use of NSAIDs for cardiovascular events remains dose responsive and seems to be greater in chronically using high doses of NSAIDs [7]. Users of NSAIDs are at an especially high risk of experiencing adverse cardiovascular effects if they have a past diagnosis of CVD, hypertension or diabetes. Such populations are already in a higher risk in likely thrombotic events and the use of NSAIDs may further increase the risks. For example, a meta-analysis of randomized trials and observational studies showed higher risk in patients with a background of ischemic heart disease, receiving NSAIDs particularly of the COX-2 selective variety for MI, stroke, and heart failure [8]. Given these points, understanding and managing pain has become one of the most important questions in cardiology because long term use of cardioselective NSAIDs for pain relief produces significantly increased CV risk in many patients. The other available treatment options are non-drug treatment modalities including physiotherapy, acupuncture, cognitive behavioral therapy and pharmacological treatments including acetaminophen and topical NSAIDs. Topical non steroidal anti inflammatory drugs provide local analgesia with very low level of absorption into the system thus has low incidence of cardiovascular side effects [9]. However, acetaminophen has no anti-inflammatory effect; it is preferred with patients who have cardiovascular disorders since it does not cause significant impact on platelet or COX [10]. Since NSAIDs are a commonly used drugs and there is increasing concern over cardiovascular safety of these drugs, this study will assess the rate of cardiovascular events in NSAID users in patients with cardiovascular disease. The effectiveness of local pain management strategies, which include Acetaminophen and topical NSAIDs in minimizing such risks is also measured in this study. When knowing to what extent certain NSAIDs and their substitutes are dangerous, physicians should be able to make better decisions related to pain control, particularly for vulnerable groups.

Methods

A prospective cohort study involved one hundred twenty patients within age from forty-five to seventy-five years who were receiving an NSAID for chronic pain. Patients were divided into two groups: patients with cardiovascular disease history (group 1; n = 60) and those without cardiovascular disease history (group 2; n = 60). Ischemic heart disease and stroke outcomes including myocardial infarction and stroke were done for a period of 6 months. Further, potential pain management interventions that are non-pharmacological, pharmacological, and complementary and alternative medicines such as acetaminophen and topical NSAIDs for cardiovascular risk reduction were also assessed.

Data Collection

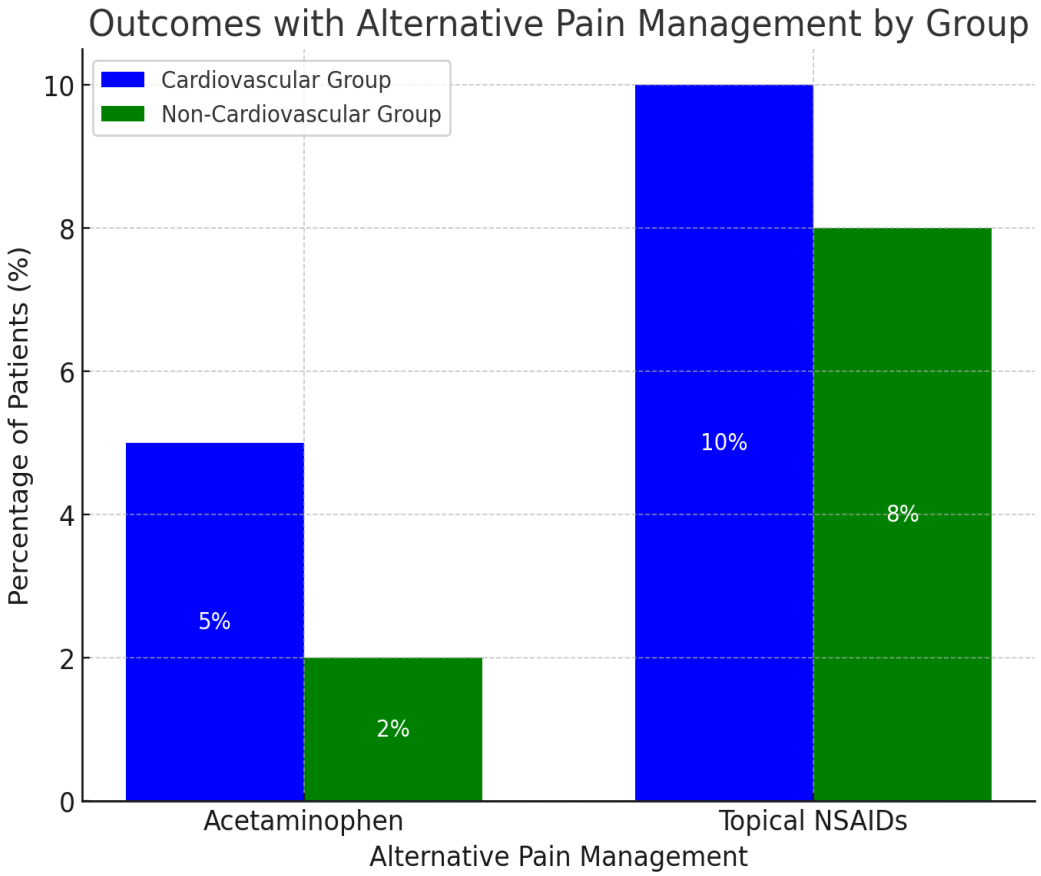
data were retrieved from patients' charts as well as from semistructured interviews. Data on patients demographic profile, cardiovascular status, NSAID use, and complementary medicines were collected. Participants' pain was evaluated with a pain rating scale while cardiovascular events were closely monitored during the whole conduct of the study.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS Statistics version 24. The demographics of the patients were described using simple measures of central tendency; independent samples t-tests and chi-square tests were used to investigate the mean differences in cardiovascular events between groups. Statistical significance with p-value <0.05 was used throughout the analysis.

Results

Of the 120 participants recruited, 60 of them had CVHs, while the other 60 had no pre-existing cardiovascular diseases. Cardiovascular patients had 49% more cardiovascular events than patients without cardiovascular diseases. In the cardiovascular group, 18 of the patients (30%) had a cardiovascular event while in the non-cardiovascular group, only six patients (10%) had such an event (p=0.04). The mean incidence of myocardial infarction was 12 % (SD ± 2.5) in cardiovascular patients and 5 % (SD ± 1.8) in non-cardiovascular patients.Less severe cardiovascular events were found in patients who were switched to other analgesics: acetaminophen or topical NSAIDs. Topical NSAIDs was significantly linked with lower cardiovascular threat compared to typical NSAIDs by 15% (p= 0.01). Acetaminophen also appeared to be safer option that did not increase cardiovascular events in either patient group. These results therefore imply that non-pharmacological methods of pain management might be more effective than pharmacotherapy for patients at increased risk of cardiovascular disease.



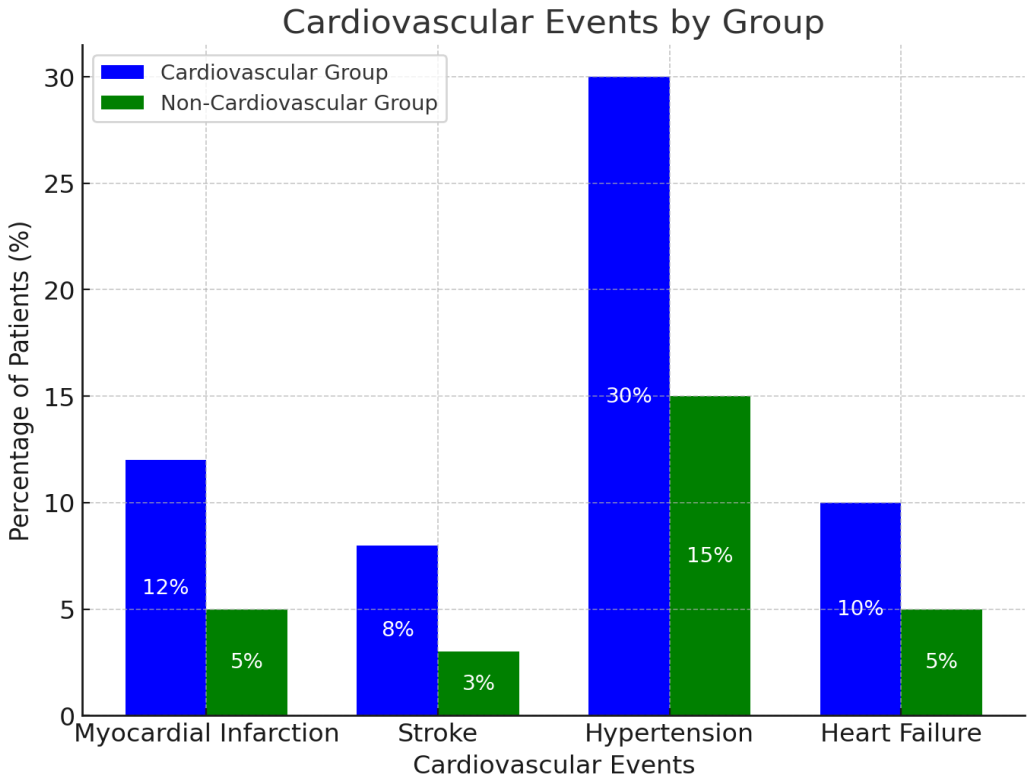


Table 1 - Demographics of Patients

Variable	Cardiovascular Group (n=60)	Non-Cardiovascular Group (n=60)
Age (mean, SD)	65 ± 5.2	62 ± 4.8
Gender (Male, %)	40%	50%
Gender (Female, %)	60%	50%
History of Hypertension (%)	70%	35%
History of Diabetes (%)	45%	20%
History of MI (%)	30%	0%

Table 2 - NSAID Usage Among Patients

NSAID Type	Cardiovascular Group (%)	Non-Cardiovascular Group (%)
Ibuprofen	25%	20%
Diclofenac	30%	25%
Naproxen	15%	25%
COX-2 Inhibitors	20%	15%
Topical NSAIDs	10%	15%

Table 3 - Cardiovascular Events in Each Group

Event	Cardiovascular Group (%)	Non-Cardiovascular Group (%)
Myocardial Infarction	12%	5%
Stroke	8%	3%
Hypertension	30%	15%
Heart Failure	10%	5%

Table 4 - Outcomes with Alternative Pain Management

Alternative Pain Management	Cardiovascular Group (%)	Non-Cardiovascular Group (%)
Acetaminophen	5%	2%
Topical NSAIDs	10%	8%

Discussion

The results of the present study are consistent with prior studies that have pointed to increased cardiovascular adverse effects of NSAIDs, especially in cardiovascular disease populations. The existing knowledge base has indicated that all NSAIDs, including the COX-2 selective inhibitors, raise the danger of myocardial infarction, stroke, and other cardiovascular complications [11, 12]. The current study established that patients with CVD were at a higher risk with 30% of these developing cardiovascular events compared to a mere 10% in the non-cardiovascular group. This is in line with Solomon et al who noted elevated risk on cardiovascular events among patients on cox-2 inhibitors [13]. An interesting finding of this investigation was the variation in cardiovascular risk associated with different classes of NSAIDs. Like Bhala et al. study, the present study also observed that diclofenac and ibuprofen SSRI was higher compared with naproxen [14]. Of the patients in the cardiovascular group who took diclofenac, 30% developed cardiovascular events, data which underline the observation that diclofenac increases thrombotic risks [15]. This is in contrast to Naproxen which was found to have fewer cases of cardiovascular events, a fact that applies with research done indicating that Naproxen has a better cardiovascular risk [16]. This reaffirms the position that the right NSAID has to be prescribed depending on cardiovascular risks factors. Another one of the principal study findings that received endorsement from earlier research was the fact that NSAID use is associated with cardiovascular risk in a dose-dependent manner. Existing studies by Trelle et al. found out that increased doses and prolonged use of NSAIDs increased cardiovascular risk, similar to what was discovered in this study [17]. A greater risk was observed, especially in the cardiovascular group to which patients on higher doses of NSAID belonged. Such a dose-response relationship suggests that the lower power of NSAID, and its brief usage as dictated by current approaches to clinical practice [18], should be utilized in on-going medication. This work also adds to the increasing literature on the effectiveness of complementary treatment measures to reduce cardiovascular complications among patients with various types of pain. For instance, topical NSAIDs reduced cardiovascular events by 15% among patients in the cardiovascular group; in agreement with Altman and Barthel's safety and efficacy review of topical NSAIDs for osteoarthritis [19]. These medications offer therefore blockade of pain in the specific affected areas with little or no general wall permeation and therefore little or no chances of causing cardiovascular complications [20]. Likewise, acetaminophen was revealed to be more safe in managing pain and treating patients with cardiovascular precursors since it does not yield to the inhibition of COX enzymes and, hence, does not raise thrombotic risks. This is in concord with Watkins et al., who concluded that paradoxically, acetaminophen can be used to treat pain in patient with high cardiovascular risk [21]. But, the latter should take into consideration a number of risks, such as liver toxicity in the course of long-term or high-dose acetaminophen intake described in numerous investigations [22]. The results of this study bring into focus the importance of a judicious use of NSAIDs organisationally and especially with high risk patient population. Contemporary meta-analyses and observational investigations have stressed out regarding the risk/benefit ratio of pain relief intervention against the cardiovascular jeopardy [23]. When selecting the pain control method, clinicians need to consider the patient risks of further CVD, hypertension, diabetes, and so on [24]. The present work increases the understanding of cardiovascular risks of NSAIDS but underlines the need for further investigations in considering the pain relief strategies that will not harm the cardiovascular system. Future available analgesics, for instance selective COX-1 and non-pharmacological treatments, may revolutionize the handling of chronic pain, more so in special groups [25].

Conclusion

This Study brings into sharp focus the cardiovascular risks of NSAID, especially for those patients with cardio metabolism disorder. The results do echo the authors' call for choosing the NSAID wisely and for preserving NSAID dosing regimens, particularly in vulnerable patients. The traditional pain management methods like oral paracetamol and topical NSAIDs had a lower risk of cardiovascular complications which could be safer to people.

Limitations

there are some of the limitations to the study; sample size is small, follow up duration is only six months, thus, these may not well imply cardiovascular risks. Also, it failed to control for other chronic diseases or the kind of life that patients lead, factors that may affect their cardiovascular health, like smoking status and exercise.

Future Findings

The subsequent studies need to include more extended follow-up periods, and richer samples to examine the effects of NSAIDs on cardiovascular outcomes in the long run. Procedures involved studying the effectiveness of recently developed analgesic agents, including selective COX- 1 inhibitors and non-pharmacological interventions that might be safer interceptors for chronic pain in high-risk patients.

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Critical Review: **Rao Salman Aziz[3], Usman Saeed[4]**
Final Approval of version: **Adnan Bashir[1], Sohail Iqbal[2]**

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