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Use of NSAIDs and the risk incidence of cardiac arrhythmia

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Atrial fibrillation is a common cardiac arrhythmia that has many risk factors including some medications; however, the effect of non-steroidal anti-inflammatory drugs (NSAIDs) and its risk is not well assessed. This study was conducted to find out if there is an association between the use of non-steroidal anti-inflammatory drugs and risk of atrial fibrillation. The study was conducted at Al-Hussein Medical City Hospital in Karbala-Iraq as a retrospective c6ase-control study between September 2014 and March 2015; including 90 patients with atrial fibrillation and 90 control subjects who were age and sex matched, and based on risk-set sampling. Current use of NSAID was started within one month and chronic use for more than one month was recorded. The current use of NSAIDs by patients with atrial fibrillation was found in 43 patients out of 90 (47.7%) of which new users were 29 (32.2%) and chronic users were 14 (15.5%), while it was found in 27 out of 90 (30%) of the control subjects who were current users of NSAIDs. That difference was statistically significant (p-value was 0.015), the odds ratio (OR) was 2.135 and 95% confidence intervals (CI) was 1.16-3.94. This study suggests that the current use of NSAIDs might be associated with increased risk of incidence of atrial fibrillation.

Key words: Non-steroidal anti-inflammatory drugs, atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac rhythm disorder observed in clinical practice that usually requires hospital admission. It is defined as a tachyarrhythmia characterized by predominantly uncoordinated atrial activation with consequent deterioration of atrial function (National Collaborating Centre for Chronic Conditions (UK), 2006).

It occurs generally due to abnormal electrical signals generated all over the atria, resulting in a quavering fibrillating atrial activity which leads to inadequate emptying of the atria. Consequently, the ventricular rate will be fast, chaotic and irregular which will also affect the emptying of the ventricles (Allessie et al., 2001).

The prevalence of AF doubles during each advancing decade of life, from 0.5% at the age of 50s to above 10% at the age of 80s (Heeringa et al., 2006). It is usually associated with increasing mortality and morbidity, mainly due to hemodynamic impairments that aggravate or even cause heart failure (Stevenson et al., 2004), and the increased risk of thromboembolic stroke resulting

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from stagnation of blood in the atria due to incomplete emptying (Wolf et al.,1991). There are many reported risk factors for AF (Rosiak et al., 2010):

1) Age; 2) hypertension; 3) heart diseases which include coronary artery disease, valvular heart disease, rheumatic heart disease, heart failure, cardiomyopathy, congenital heart disease, and pericarditis; 4) lung diseases such as chronic obstructive pulmonary disease (COPD) and pulmonary embolism; 5) hyperthyroidism; 6) other health conditions such as obesity, diabetes, renal failure and metabolic syndrome; 7) family history of AF and heart diseases; 8) external factors such as drinking too much alcohol, caffeine and other stimulants, smoking, and also psychological stress, fatigue and illness; 9) medications such as high-dose steroid therapy (Felson et al., 1988).

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for treatment of pain and inflammatory conditions. The non-selective NSAIDs are known to cause gastrointestinal adverse effects (Laine, 2002) mostly by inhibiting cyclooxygenase (COX)-1 mediated production of prostaglandins, in addition to a range of nephrotoxic disorders (Whelton, 2001). The selective COX-2 inhibitors have improved gastrointestinal effect profile (Laine, 2002), but their renal and cardiovascular safeties are often of concern because both renal (Whelton, 2001) and cardiovascular (Trelle et al., 2011; Aw et al., 2005) risks are frequently reported.

The use of both selective and non-selective NSAIDs may increase the risk of atrial fibrillation mainly through their renal and cardiovascular adverse effects; like fluid retention, electrolyte disturbances and blood pressure destabilization (Whelton, 2001; Trelle et al., 2011), but the evidence for such effects is still limited (Zhang et al., 2006; De Caterina et al., 2010).

So, confirming the association between the use of NSAIDs and the incidence of atrial fibrillation would have major clinical and public health consequences (Zhang et al., 2006), especially for older people because of the prevalent use of NSAIDs and the higher incidence of AF (De Caterina et al., 2010).

However, many confounding factors may increase the risk of AF, particularly by the underlying inflammatory disorders that lead to the use of NSAIDs (Engelmann et al., 2005).

The aim of this study was to find out if there is an association between the use of NSAIDs and the risk of incidence of the most common cardiac arrhythmia, atrial fibrillation.

METHODS

Study design

A retrospective case-control study was conducted in Al-Hussein Medical City Hospital in Karbala - Iraq. Patients with atrial fibrillation and control subjects were selected from the medical wards, the cardiac care unit (CCU) and from the outpatient clinic in the period from October 2014 to April 2015.

Case definition and inclusion criteria

Ninety adult patients (50 males and 40 females) were selected randomly with a diagnosis of acute atrial fibrillation, who were admitted to the CCU. Patients with chronic AF were excluded. In addition to that, 90 control subjects (54 males and 36 females) were selected randomly from the medical inpatients and outpatients departments using risk-set sampling, who share the same risk factors for AF as the patients group.

Data collection

A questionnaire was used to collect data from both patients and controls groups. A full medical history and medication history was taken from patients and control subjects. Age, sex, and body mass index (BMI) were recorded. Since there is a number of risk factors for AF that can also be associated with the use of NSAIDs (Engelmann et al., 2005), data was obtained from patients and controls on any previous history of disorders that may increase the risk of AF. Co-morbidities were also identified and recorded.

NSAIDs use

The current use of non-steroidal anti-inflammatory drugs (NSAIDs) was reported in both groups. The current users of NSAIDs were categorized into two groups: “new users” defined by having redeemed their first use within few days to 1 month, and “long term or chronic users” with chronic conditions such as arthritis that have been taking NSAIDs for a long time (more than 1 month). The use of NSAIDs which include non-aspirin non-selective NSAIDs (e.g. ibuprofen, diclofenac, naproxen, ketoprofen, meloxicam, piroxicam and mefenamic acid), and selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, valdecoxib, and etoricoxib) were recorded for both patients and control subjects.

Statistical analysis

The study variables are presented as means ± standard deviations (SD), and as numbers and percentages in contingency tables. Data was recorded and analyzed by using conditional logistic regression to calculate the odds ratios (OR) for atrial fibrillation among current users of NSAIDs, and T-test was used for continuous variables. *P-value* of < 0.05 was considered as significant.

RESULTS

Table 1 shows the demographic characteristics of patients and control subjects. There was obviously no significant difference between AF patients and control subjects regarding age, sex and BMI, so they are considered as matched groups. Table 2 shows age distributions among patients and control subjects:

Patient in the age range of 51-90 are the most exposed to AF and result in having greater risk for the disease, younger patients in the age range of 21-50 have lower incidence of AF, and control subjects with age range of 41-70 are the highest with other diseases that had great risk factors for AF. Table 3 shows the risk factors of AF

Table 1. Demographic characteristics of patients and control subjects.

Characteristics	AF patients	Controls	*P-value*
Age (mean ±SD)	61.4 ±15.2	60.3 ±14.6	NS
Sex (male %)	55.5%	60.0%	NS
BMI (mean ±SD)	26.7 ± 4.4	26.4 ± 4.2	NS

Table 2. Age distributions among patients and control subjects.

Age groups	AF Patients		Controls	
	No.	%	No.	%
21-30	2	2.2	3	3.3
31-40	4	4.4	6	6.6
41-50	14	15.5	16	17.7
51-60	31	34.4	29	32.2
61-70	20	22.2	24	26.6
71-80	10	11.1	8	8.8
81-90	9	10	4	4.4
Total	90	100	90	100

Table 3. Risk factors for AF among patients and control subjects.

Risk factors	AF Patients		Controls	
	No.	%	No.	%
Obesity	58	64.4	42	46.6
HT	54	60.0	50	55.5
Smoking	51	56.6	40	44.4
CHD (IHD)	28	31.1	24	26.6
DM	26	28.8	27	30
Family Hx.	24	26.6	18	20
CHF	18	20.0	20	22.2
Lung dis.	10	11.1	12	13.3
Hyperthyroid	7	7.7	3	3.3
CRF	6	6.6	5	5.5

Each subject may have more than one risk factor.

among patients and control subjects:

The most frequent risk factors that are found to be associated with AF were obesity 64.4%, hypertension 60% and smoking 56.6%. Other risk factors were: diabetes mellitus, coronary heart disease, congestive heart failure, chronic renal failure, lung disease, hyperthyroidism and family history of arrhythmia and heart diseases which have variable percentages in both patients and controls.

Table 4 shows the current use of NSAIDs among AF cases and control subjects. The current users of NSAIDs among AF cases was 43 patients (47.7%); of which the new users were 29 out of 43 (67.4%) and the chronic users were 14 out of 43 (32.6%) as shown in Figure 1, while the current users of NSAIDs among control cases was 27 subjects (30%); of which the new users were 19 out of 27 (70.3%) and the chronic users were 8 out of 27 (29.7%) as shown in Figure 2.

Table 4. Current use of NSAIDs among AF cases and control subjects.

NSAIDs use	AF Cases		Control	
	No.	%	No.	%
Current use*	43	47.7	27	30
New users	29	67.4	19	70.3
Chronic users	14	32.6	8	29.6
No use	47	52.3	63	70
Total	90	100	90	100

* Odds ratio (OR) = 2.135; 95% Confidence intervals (CI) = 1.16 to 3.94; Z score = 2.4; P value = 0.015.

The odds ratio (OR) of AF among the current users of NSAIDs was 2.135, and 95% confidence intervals (CI) was 1.16 to 3.94. This was statistically significant (p-value was 0.015).

DISCUSSION

The most common cardiac arrhythmia worldwide that usually requires CCU admission is atrial fibrillation (AF). It is commonly associated with increased long term risk of stroke, heart failure and death (Fuster et al., 2011).

The risk of AF is known to increase with age. In the elderly, slow heart rate which is mainly due to underlying alterations in autonomic tone and/or subclinical sino-atrial node dysfunction may potentially predispose older patients to escape rhythm, thus associated with an increased risk of AF (Benjamin et al., 2009). Therefore, older patients with age above 55 have more frequency of AF reaching about 70% as observed in this study.

Hypertension is a well-known risk factor for new-onset AF. Besides, other important cardiovascular risk factors, such as obesity, hyperlipidemia and cigarette smoking are less clearly related to the incidence of AF (Huxley et al., 2011). Obesity also as a risk factor of AF is strongly associated with osteoarthritis, which is one of the most common indications for NSAIDs and also the risk seemed to be higher in older people (Felson et al., 1988; Holliday et al., 2011).

After adjustment for age, sex, BMI and some other risk factors for AF among cases and controls, there was a statistically significant increase in the incidence of AF with the current use of NSAIDs. It was found that the odds ratio (OR) for AF among current NSAID users was 2.135 with 95% confidence intervals (CI) 1.16 to 3.94, which

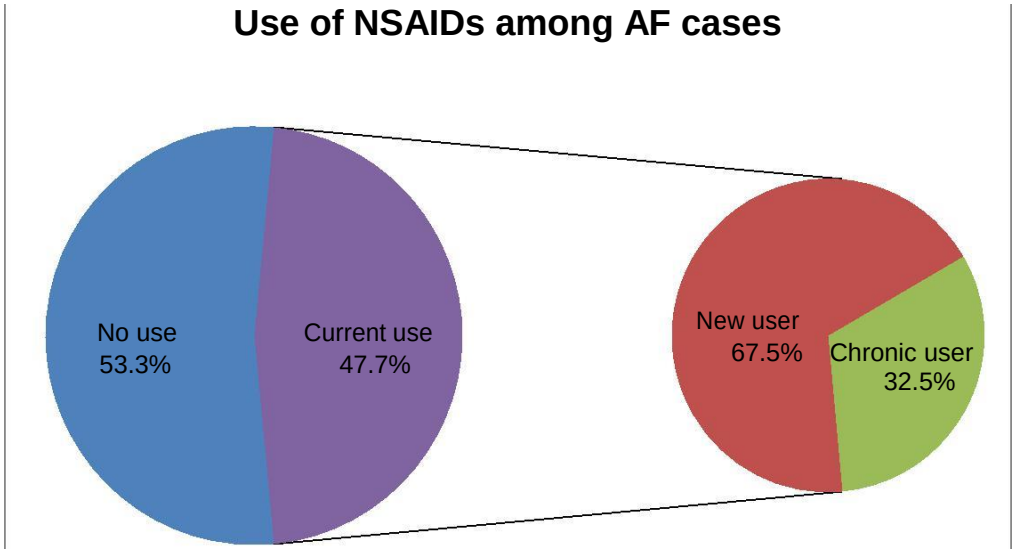

Figure 1. The current use of NSAIDs among AF patients.

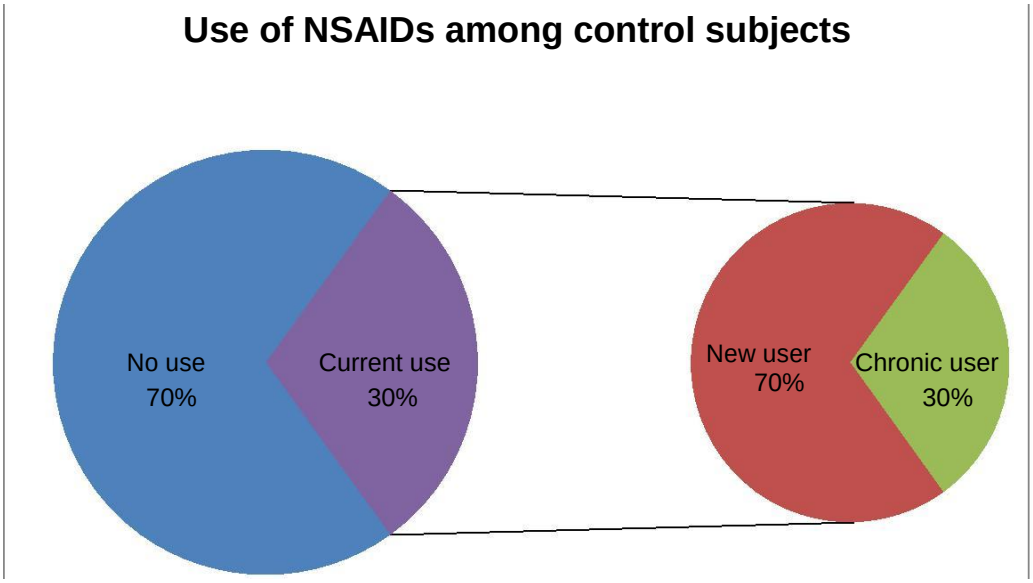

Figure 2. The current use of NSAIDs among controls subjects

means that the risk of incidence of AF was about twice more in NSAIDs users.

These findings were comparable with that observed by other case-control study which found that the incidence rate ratio associating the current use of NSAIDs with AF was 1.33 (95% CI 1.26 to 1.41) for non-selective NSAIDs and 1.50 (1.42 to 1.59) for selective COX-2 inhibitors as compared to non-users (Schmidt et al., 2011).

Another follow-up study reported that the current use of NSAIDs was associated with increased risk of AF as compared to never-use (hazard ratio (HR) was 1.76, 95% CI 1.07 to 2.88) . Moreover , recent past use (within 30 days after discontinuation of NSAIDs use) was associated with an increased risk of AF as compared to never-use (HR was 1.84, 95% CI 1.34 to 2.51) when adjusted for age, sex and other potential confounders (Krijthe et al., 2014).

Furthermore, the newer and the chronic users of NSAIDs were recorded in this study. The percentages of newer users, who use NSAIDs for less than 1 month, and the chronic users, who use NSAIDs for more than 1 month, were nearly the same in both AF patients and control subjects with no statistically significant difference.

Although, there other studies reported an association between the use of NSAIDs and the risk of AF (De Caterina et al., 2010; Schmidt et al., 2011; Krijthe et al.,

2014), still this association between NSAIDs use and occurrence of AF does not indicate a cause and effect relation. One proposed explanation for this association may be the presence of an underlying inflammatory condition that increase the risk of AF on one hand and prompt the use of NSAIDs on the other hand (Engelmann et al., 2005; De Caterina et al., 2010).

Another explanation is that the use of NSAIDs may increase the risk of AF through renal and cardiovascular related effects. Some patients who are treated with NSAIDs may experience nephro-toxic disorders. Since both COX enzymes are present in kidney tissue, the inhibition of prostaglandin synthesis by both COX derived routes retreat inflammation and disturb a variety of physiological processes (Whelton, 2001). These changes may lead to increase in blood pressure due to expansion of plasma volume, increase peripheral vascular resistance, attenuation of diuretic and antihypertensive drug effects, and fluctuation of serum potassium and sodium (Whelton, 2001; Aw et al., 2005). Therefore, the increased risk of AF among NSAIDs users may be attributable to these adverse renal and cardiovascular effects of NSAIDs, which can subsequently trigger atrial fibrillation (Van der Hooft et al., 2004).

CONCLUSION AND RECOMMENDATIONS

This study suggests that there could be an association between the use of NSAIDs and risk of incidence of atrial fibrillation.

So, NSAIDS should be used very cautiously in older patients and especially those with a history of risk factors for AF, who are already at higher risk for adverse effects of these drugs, regardless of whether an association between NSAIDs use and AF do exist.

Furthermore, it is recommended to monitor the users of NSAIDs for the occurrence of AF especially in patients who have other risk factors.

Conflict of Interests

The authors have not declared any conflict of interests.

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