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USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN THE PROPHYLAXIS OF ATRIAL FIBRILLATION POST CARDIAC SURGERY

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Keywords:

Nonsteroidal anti-inflammatory drugs, Atrial fibrillation, prophylaxis, CABG, ECG

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Abstract

Background:

Atrial fibrillation (AF) is the most common postoperative complication following cardiac surgery, with incidence of (20 – 50 %) was reported. its occurrence has been linked to the inflammatory process post cardiopulmonary bypass.

Objectives:

To test whether nonsteroidal anti-inflammatory drugs could reduce the incidence of atrial fibrillation post cardiac surgery.

Double blind, randomized study conducted at Queen Alia Heart Institute from June 2014 to June 2015 on 200 patients who underwent elective first time coronary artery bypass grafting. Patients were divided into two equal groups; one group of patients was given 400mg of Ibuprofen three times daily while the other group received conventional treatment. The primary end point was the incidence of atrial fibrillation.

Results:

Atrial fibrillation occurred in 12% of the treatment group in contrast to 27% in the control group P value <0.05%.

There was 51.8% decrease in the incidence of AF. The length of hospital stay was found to be significant statistically between the two groups. 4.6 ± 1.3 for the ibuprofen group VS 6.2 ± 2.8 for the control group P <0.05%

Conclusion:

Use of nonsteroidal anti-inflammatory drugs such as Ibuprofen was found to be relatively safe and effective in reducing the incidence of post-operative atrial fibrillation in patients undergoing elective coronary artery bypass grafting

Introduction

Atrial fibrillation(AF) is the commonest complication seen after coronary artery bypass grafting(CBAG) (1,2). It occurs in 25-40% of the patients undergoing CABG (3,4,5,6,7), and even up to 62% when combined with valve procedure (6). Atrial fibrillation is associated with hemodynamic compromise, increased likelihood of thromboembolism and stroke with consequent prolonged Hospitalization and obvious increase of hospital morbidity (7,8,9). Consequently, it is pretty essential to prevent and avoid such a harmful complication.

AF commonly occurs at 0-4 days (10,11), with the peak incidence on the second to 4th day postop (4) at a time when the inflammatory process related to bypass surgery is at its peak with less hemodynamic stress (4). This generalized inflammatory response is associated with leukocyte and complement activation, high levels of C-reactive proteins and interleukin-6 (4,5,7). Many clinical studies have shown that the above mentioned vascular markers are

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significant higher in patients with AF in contrast to patients without, which support the inflammatory hypothesis behind the postoperative atrial fibrillation (4,5,7).

Therefore, anti-inflammatory drugs such as non-steroidal agents might reduce the incidence of postop. AF. We performed prospective, double blinded, randomized trial to verify Ifubrofen (non-steroidal anti-inflammatory drug) can lower the incidence of AF after CABG by decreasing the degree of the inflammatory response.

Methods

This was a prospective randomized controlled study that was conducted at Queen Alia Heart Institute (Amman, Jordan) between June 2014 and June 2015. The study protocol was approved by the Jordanian royal medical services local ethical committee. There were 200 consecutive patients scheduled to undergo their first on – pump CABG.

A total of 320 patients were screened with 110 excluded from the study as well 10 patients who refused to be enrolled in the study.

Inclusion criteria consisted of elective first time CABG, use of β-adrenergic blockade. And normal sinus rhythm. Exclusion criteria included history of AF episodes or flutter or otherarrhythmias, patients who underwent cardiac surgery without using cardiopulmonary bypass, Patient with serum creatinine more than 132.6 µmol/L, and those with history of gastro intestinal bleeding.

The study's primary end point was the hemodynamic instability due to AF regardless of episode duration. Secondary end points were the length of hospital stay and adverse effects of non-steroidal anti-inflammatory drugs. All patients in the Ibuprofen and controlled groups underwent the complete protocol of the intended treatments until designated end points, so intention was the same as treatment. After anyepisode of AF, the study protocol was discontinued.

The age, history of hypertension or diabetes mellitus, total pump time and aortic cross clamp time, hospital stay duration were recorded. The protocol was double – blinded, in which the surgical staff, principals investigators, and patients were blinded to the assigned therapy, clinical data were collected and recorded in the data base by independent blinded investigators.

Randomization lists were sent to the department of pharmacy where the drugs were prepared. The investigator sent the name and date of birth, each time a new patient had given informed consent.

Randomization was performed on the operation day, the pharmacist selected the next number on the randomization list, labelled the drug container to the department where the patient was treated. all patients were randomized into either the study or control group, had normal sinus rhythm prior to the surgery.

Patients were divided into two major equal groups, each consisted of 100 patients i.e. the ibuprofen group (study group) and control group. Ketorolac was started as soon as the patients arrived in the intensive care unit and given as 30mg intravenously every 6 hours until the patient was able to take oral medications then the patient was switched to ibuprofen 400mg P.O three times a day for a total of 7 days or until discharge if it was before 7 days.

patients stopped receiving either choice if AF occurred. Regarding general anesthesia surgical techniques and patient monitoring were standardized for all patients. All patients were monitored with continuous ECG monitoring (telemetry) for the first 2days past operatively either in ICU1 or stepdown ICU2:
Values are presented as means ± standard deviation and percentage.

Chi-Square was used to analyze the results differences were considered to be statistically significant when P value <0.05. in addition to that the test was used for comparison of patients in terms of duration of hospitalization.

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Results:

The demographic data did not differ significantly between the two groups. The mean age of the treatment and control group was comparable 67.1 VS 62.1 years respectively as well as the gender, 73% VS 71% being Males.

Hypertension was found in 64% (64 patients) of the Ibuprofen group and in 62% (62 patients) of the control group. DM was found in 42%, 39% of the Ibuprofen and control group respectively.

With respect to mean aortic cross clamp time in the Ibuprofen
56.32 ±14.12 minutes VS 55.1 ± 12.9 minutes in the control group whereas the average total pump time was 101.4 ± 19.4minutes in the Ibuprofen group VS 13.2 ±21.2minutes in the control group. Both parameters were found to be statically non-significant ($P > 0.05$)

See table 1 ,2.
The incidence of postoperative AF was 13% (N = 13) in the ibuprofen group while it was 27% (N = 27) in the control group, which is statically significant ($P < 0.05$)

Concerning the length of hospital stay, it was 4.7± 1.3 in the Ibuprofen group VS 6.2 ± 2.8 in the control group, which was found statistically significant. Also, it was found that the duration of AF episode was less in the Ibuprofen group when compared to the control group with significant value.

The results of our study are summarised in the below scheme.

Discussion

Several studies demonstrated that the inflammatory response to cardiopulmonary bypass following CABG is linked to post-operative AF[11,12,13].

Bruins et al [12] found biphasic complement activation, with the first phase during the surgery itself while the other one happens during the first 5days after surgery with resulting obvious rise in CRP levels.

Moreover,chung et al [13] also showed significant rise of CRP levels in patients with AF. In addition to that, Dernellis et al [14] came up with fact that the paroxysmal AF is related to an inflammatory process boosted by the high levels of CRP seen following cardiacsurgery.

Prophylactic nonsteroidal anti-inflammatory drugs reduced the incidence of AF following coronary artery bypass grafting by 65% in the first randomized trial to data conducted by cheruku and his colleagues to study the effects of anti-inflammatory medications on the prevention of AF after CABG [4]. In our study, it was found to be approximately 51.8% decreased risk of developing AF in patients undergoing isolated CABG.

Cheruku and his colleagues [4] randomized one hundred patients to two groups: one received 30mg ketorolac intravenously 6 hours until able to take oral medication, at which points the patients were switched to 600mg Ibuprofen orally three times daily; the other group received conventional treatment AF occurred in 28.6% of the conventional treatment group while it occurred in 98% of the Ibuprofen group.

However, Horbach and his colleagues conducted first double-blind, Randomized clinical trial to analyze the effects of naproxen on post-operative AF [7], He found that naproxen did not significantly reduce the incidence of post-operative AF in patients given naproxen and underwent isolated CABG. There was 55% decrease in the incidence of AF, but it was not statistically significant. But, there was significant reduction in the duration of AF. Due to the significant increase in the incidence of acute renal failure, the study was prematurely stopped.

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A non-steroidal anti-inflammatory drug was selected based on the proposed role of inflammatory in the etiology of post-operative AF after CABG[7]. Mathew et al, found in prospective observational study on 4657 patients that non-steroidal anti-inflammatory drugs was associated with reduced incidence of atrial fibrillation (AF)[15].
We noticed that the patients in the Ibuprofen group who developed AF had episodes with shorter duration in comparison to the control group, this might be explained by the anti-inflammatory effects of Ibuprofen on the frequency and duration of AF, no difference between the two groups in the number of AF episodes. However, in cheruku study [4], there were shorter duration of AF episodes but more episodes of AF in the Ibuprofen group. Short duration of AF episode was also seen in the naproxen study [4].

The analgesic effects of Ibuprofen could decrease the sympathetic tone due to pain stimuli with consequent decrease in the incidence of AF [4].

The observed short duration of AF episodes could potentially decrease the incidence of adverse events [7], which favours the use of prophylactic Ibuprofen following cardiac surgery.

Ibuprofen use was not associated with any significant morbidity when compared with the control group. 5patients developed acute kidney injury (defined as an increased ≥50% in postoperative creatinine) compared to 2 patients in the control group which was not statistically significant.

The same finding was found by cheruku [4] and his colleagues, however horbach and his colleagues [7] had to stop the trial after they had high incidence of post-operative renal failure.

The dose of Ibuprofen used in our study was less than the one used in either of the previous two studies which might explain our results despite our strict definition of acute kidney injury. With regard to gastrointestinal complication, only two patients had significant gastrointestinal bleeding requiring blood transfusion and discontinuation of Ibuprofen. These results might be related to the lower dose of Ibuprofen as well the routine use of prophylactic proton pump inhibitor omeprazole 40mg once daily.

In addition to that, the length of hospital stay was found to be less in the Ibuprofen group and statistically significant. This might be related to the impact of AF on the patient's general status requiring more care.

Study limitations

First limitation is the absence of continues ECG monitoring except for the first and second day for both the treated and the control group, after that the arrhythmia was usually detected either by early morning ECG or symptomatic patients with clinical signs or even asymptomatic accidental findings.

Second limitation is that all patients included in this study underwent coronary artery bypass grafting excluding the value surgery which has originally more incidence of AF.

Conclusion

Use of non steroidal anti-inflammatory drugs post operatively such as Ibuprofen was found to be relatively safe and effective in reducing the incidence of post-operative atrial fibrillation in patients undergoing elective coronary artery bypass grafting with no significant morbidities and obvious decrease in the length of hospitalisation.

Table 1 demographic and clinical characteristics:

Variable	Ibuprofen (100)	Control (100)	P value
Age	61.7 ± 9.5	62.1 ± 8.7	NS
Male	73	71	NS
Female	27	29	NS
HT	64	62	NS
DM	42	39	NS

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Table 2 intraoperative and postoperative characteristics of patients:

Variable	Ibuprofen (100)	Control (100)	P value
TPT *	101.4 ± 19.4	103.2 ± 21.2	NS **
TPT in patients with AF	102.5 ± 19.5	103.1 ± 20.5	NS
ACX ^	56.2 ± 13.25	55.1 ± 12.9	NS
ACX in patients with AF	57.32 ± 14.12	55.2 ± 13 .91	NS
Patient with AF	13	21	P <0.05 significant
Patient with acute kidney	5	2	NS
Patient with gastro-intestinal bleeding	2	0	NS

*: total pump time
**: none-significant
^: aortic cross clamp

Table 3 duration of atrial fibrillation and length of hospital stay

Variable	Ibuprofen group (100)	Control (100)	P
Length of hospital stay	4.7 ± 1.3	6.2 ± 2.8	P < o.o5
Duration of AF	0.65 ± 3.25	4.3 ± 12.1	P < 0.05

The result of our study was summarized in the below scheme:

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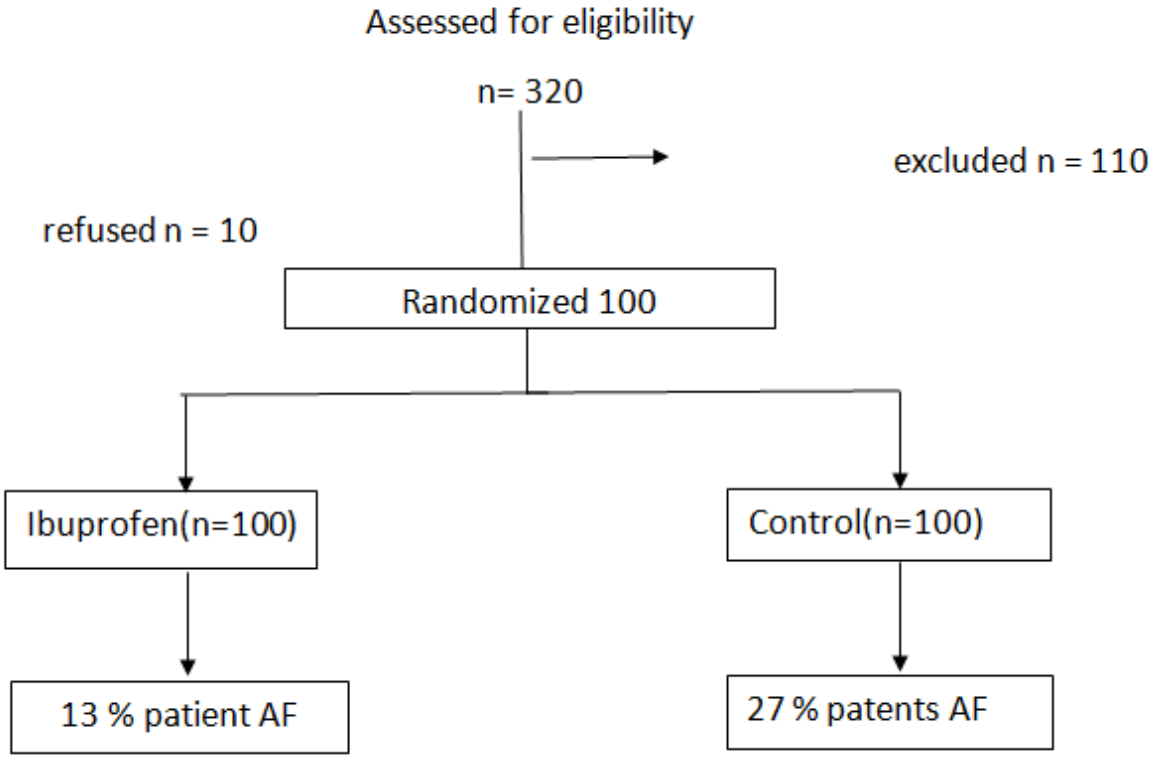

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