Low Dose Inhaled Corticosteroid in Asthma & Prevention of Acute Coronary Syndrome

MMJ 2010; 9(1):57-62

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Abstract:

Background: Asthma is associated with higher risk of adverse cardiovascular outcomes. Hypoxemia and inflammation had been suggested to play a role and the use of inhaled corticosteroids is possibly associated with a major effect on reduction this higher risk with amelioration of the suggested mechanisms.

Objective: This study had been designed to assess the effect of the use of low dose inhaled corticosteroids on the frequency of myocardial infarction in asthmatic patients, compared to the effect of other anti-asthmatic medications.

Methods: This study is a prospective study that included 92 asthmatic patients who had unstable angina at the time of inclusion. The sample were randomly selected from those who had been admitted to the coronary care unit of Al-Yarmouk Teaching Hospital during the period between February 2008 to February 2009, with the mean period of follow up of 8.3± 2.1 months (6 months-1 year). Detailed medical history had been taken and thorough physical examination was made for all patients. The patients had been sub-classified according to the type of the used therapy for asthma.

Results: Twenty three male and 69 female patients had been enrolled in this study. The mean age was 52.48 ± 9.86 and 50.36 ± 6.8 year-old for male and female patients, respectively. After 1 year of follow up 17 patients (18.5% of the sample) had myocardial infarction during the period of follow up, the rest of the sample (75 patients, 81.5% of the sample) completed their period of follow up without any evidence of having myocardial infarction. Sixty patients had been treated with inhaled corticosteroid therapy (65.2%), while 20 patients (21.7%) and 12 patients (13%) had been treated with inhaled B2 agonist therapy alone and inhaled B2 therapy in addition to leukotrien receptor antagonist therapy, respectively. Nine out of the 17 patients (52.9% of those with MI) were 40-49 year-old. Only 5 out of the 60 patients who had been treated with inhaled corticosteroid therapy (29.4% of those having MI, 8.3% of those treated with inhaled corticosteroid therapy) had myocardial infarction during their follow up. This study revealed that 5 out of 17 patients with evidence of acquiring myocardial infarction during the period of follow up (29.4%) had at least one marker of asthma severity. Only 2 out of 18 patients with any marker of asthma severity had used low dose inhaled corticosteroid (11.1%), while the rest of them (16 patients, 88.9% of those with any marker of severity) were using other anti-asthmatic medications.

Conclusion: The use Low dose inhaled corticosteroid was associated with decreased frequency of acute myocardial infarction in asthmatic patients initially diagnosed to have unstable angina in comparison to the frequency of MI among patients treated with other anti-asthmatic medications. MI was more frequent among younger asthmatic patients. Having any marker of asthma severity is associated with higher risk of having myocardial infarction. Having any marker of asthma severity is associated with higher risk of having myocardial infarction. Use of low dose inhaled corticosteroid is associated with less severe asthma and lower frequency of developing acute myocardial infarction.

Keywords: inhaled, corticosteroids, asthma, myocardial, infarction, prevention

Introduction:

Most deaths from asthma are preventable, particularly those among young people. Nonetheless, the rate of death from asthma is between less than 1- 4 per 100,000 per year among the general population worldwide and up to 10 per 10,000 per year among people with asthma in Canada who take medications. [1,2] The rate of death from asthma, which increases markedly with the severity of asthma,[3] nearly doubled in the United States during the 1980s.[4]

The efficacy of inhaled corticosteroids in reducing airway inflammation and hyperresponsiveness has led to their widespread use as initial therapy in the treatment of moderate-to-severe asthma in adults. These drugs are very effective in reducing the frequency of days with symptoms, improving lung function, and reducing the frequency of hospitalization for asthma and the risk of a life-threatening attack. [5-9]

Asthma patients may be at increased risk of adverse cardiovascular outcomes for several reasons. Hypoxia- induced release of catecholamines can lead to tachycardia, hypertension, and an increase in shear stress on arterial walls [10]. Shear stress has been linked to an increased tendency for atherosclerotic plaque to rupture [11,12]. Catecholamines may also increase cardiac risk through the direct activation of platelets, making ruptured plaques more susceptible to thrombosis [13,14].

Some asthma medications may also add to the risk of cardiovascular events. A two fold increase in cardiac mortality has been observed in patients treated with inhaled or oral formulations of beta-agonists and theophylline, especially in those with a history of coronary artery disease [15]. In addition, excess cardiac risk from hypoxic episodes may be a consequence of demand ischemia and infarction of cardiac muscle supplied by coronary arteries with flow-limiting but stable atherosclerotic plaques.[16]

Advocates for inhaled corticosteroids argue that chronic beta agonist therapy may be harmful by providing symptom relief while permitting the underlying inflammatory process to progress. [17-19].

Although some studies found no difference when inhaled corticosteroids were compared to monotherapy with long-acting beta agonists (LABA) [20], most studies favored inhaled corticosteroids over chronic beta agonist therapy [21-22]. This is illustrated by the following studies: In a double-blind, controlled trial, 103 patients with newly detected asthma were randomly assigned to receive inhaled corticosteroid (budesonide) or chronic beta agonist (terbutaline) [21]. Budesonide was more effective at reducing symptoms, decreasing rescue beta agonist administration, and improving peak expiratory flow rate (PEFR). In a double-blind, controlled trial, 241 children with asthma were randomly assigned to receive a chronic long-acting beta agonist (salmeterol), an inhaled corticosteroid (beclomethasone), or placebo [22]. Beclomethasone was associated with decreased airway responsiveness to methacholine, decreased need for rescue beta agonist, and fewer asthma exacerbations compared to salmeterol or placebo. [22]

This study had been designed to assess the effect of the use of inhaled corticosteroids on the frequency of myocardial infarction in asthmatic patients and compare between the frequency of myocardial infarction in different kinds of asthma medical therapy.

Patients and Methods:

This study is a prospective study that included 92 asthmatic patients who had unstable angina at the time of inclusion. The sample were randomly selected from those who had been admitted to the coronary care unit of Al-Yarmouk Teaching Hospital during the period between February 2008 to February 2009, with the mean period of follow up of 8.3± 2.1 months (6 months-1 year). Detailed medical history had been taken and thorough physical examination was made for all patients. The patients had been sub-classified according to the type of the used therapy for asthma.

Result:

This study had included 92 asthmatic patients whose mean age was 50.89 ± 7.69 year-old (40-70 year-old). Twenty three male and 69 female patients had been enrolled in this study. The mean age was 52.48 ± 9.86 and 50.36 ± 6.8 year-old for male and female patients, respectively. Ten out of 23 male patients (43.5%) were in their fifth decade of life while 32 out of 69 female patients (46.4%) were in this age group. Figure-1 and table-1 show patients' age and gender distribution.

Age groups	***Male***		***Female***		***Total***	
	No.	***%***	***No.***	***%***	***No.***	***%***
40-49 year-old	10	43.5%	32	46.4%	42	45.7%
50-59 year-old	7	30.4%	27	39.1%	34	37.0%
≥ 60 years	6	26.1%	10	14.5%	16	17.4%
Total	***23***	***100%***	***69***	***100%***	***92***	***100%***

This study revealed that after 1 year of follow up 17 patients (18.5% of the sample) had myocardial infarction during the period of follow up, the rest of the sample (75 patients, 81.5% of the sample) completed their period of follow up without any evidence of having myocardial infarction. Figure-2 shows patients' distribution according to the frequency of Myocardial infarction.

Sixty patients had been treated with inhaled corticosteroid therapy (65.2%), while 20 patients (21.7%) and 12 patients (13%) had been treated with inhaled B2 agonist therapy alone and inhaled short acting B2 agonist therapy in addition to leukotrien receptor antagonist therapy, respectively. Figure-3 shows patients' distribution according to the used therapy.

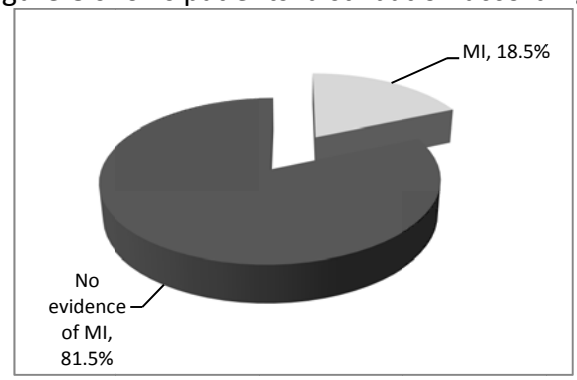

Figure-2: Patients' distribution according to the frequency of acquiring the Myocardial Infarction (MI)

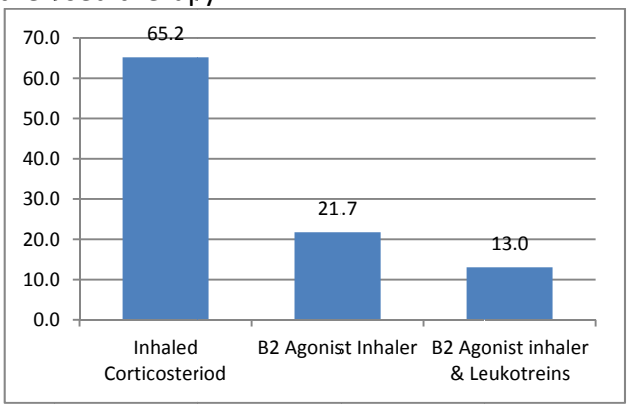

Figure-3: Patients' distribution according to used therapy

Regarding the gender distribution of myocardial infarction patients, eight out of 23 male patients (34.8% of the male patients) and 9 out of 69 female patients (13% of the female patients) had myocardial infarction during the follow up period. Statistical analysis using Chi square test showed statistically significant difference in frequency of MI between male and female with higher risk of developing MI in male patients. Table-2 & figure-4 show Patients' distribution according to their gender and frequency of acquiring MI during the follow up period.

Table-2: Patients' distribution according to their gender and frequency of MI

	Male		***Female***		***Regardless gender***	
	No.	***%***	***No.***	***%***	***No.***	***%***
MI	8	34.8%	9	13.0%	17	18.5%
No Evidence of MI	15	65.2%	60	87.0%	75	81.5%
Total	***23***	***100.0%***	***69***	***100.0%***	***92***	***100.0%***

Regarding the age distribution of those who had MI during the follow up period, this study revealed that the mean age was 48.5 ± 7.3 and 51.4 ± 7.7 year-old respectively. Nine out of the 17 patients (52.9% of those with MI) were 40-49 year-old. By the application of student's t-test to assess the statistical significance of the difference between the mean age of those who had evidence of MI and those who hadn't (p value > 0.05). Table-3 and figure-5 show patients' distribution according to their age and frequency of MI.

Table-3: Patients' distribution according to their age and frequency of MI

	Myocardial Infarction		***No Evidence***		***Total***	
	No.	***%***	***No.***	***%***	***No.***	***%***
40-49 year-old	9	52.9%	33	44.0%	42	45.7%
50-59 year-old	6	35.3%	28	37.3%	34	37.0%
60 years	2	11.8%	14	18.7%	16	17.4%
Total	17	100.0%	75	100.0%	92	100.0%

Only 5 out of the 60 patients who had been treated with inhaled corticosteroid therapy had myocardial infarction during their follow up. While 5 out of 13 patients treated with inhaled B2 agonist with leukotriens receptor antagonist had MI during their follow up. Seven patients treated with inhaled B2 agonist acquired MI during the follow up period (41.2% of those with MI). By assessing the statistical significance of the difference in frequency of MI between those who had been treated with inhaled corticosteroid and those had been treated with other types of anti-asthmatic drugs (P value < 0.05). Table-4 and Figure-6 show the sample distribution according to the frequency of MI and the type of the used therapy.

Table-4: Sample distribution according to the frequency of MI and the type of the used therapy.

	Myocardial Infarction		***No Evidence***		***Total***	
	No.	***%***	***No.***	***%***	***No.***	***%***
Inhaled Corticosteriod	5	29.4%	55	73.3%	60	65.2%
B2 Agonist Inhaler	7	41.2%	13	17.3%	20	21.7%
B2 Agonist inhaler & Leukotreins	5	29.4%	7	9.3%	12	13.0%
Total	***17***	***100.0%***	***75***	***100.0%***	***92***	***100.0%***

Fifty out of 60 female patients had been treated with inhaled corticosteroid therapy, in contrast 13out of 23 male patients had been treated with either inhaled B2 agonist alone (9 patients, 39.1% of the male patients) or inhaled B2 agonist with leukotrien receptor antagonist (4 patients,

17.4% of the male patients). Table-5 and fiure-7 show the frequency distribution of the sample according to gender and type of therapy.

Table-5: Frequency distribution of the sample according to gender and type of the used therapy.

	Male		***Female***		***Regardless gender***	
	No.	***%***	***No.***	***%***	***No.***	***%***
Inhaled Corticosteriod	10	43.5%	50	72.5%	60	65.2%
B2 Agonist Inhaler	9	39.1%	11	15.9%	20	21.7%
B2 Agonist inhaler & Leukotreins	4	17.4%	8	11.6%	12	13.0%
Total	23	100.0%	69	100.0%	92	100.0%

This study revealed that the mean age of those treated with inhaled corticosteroid therapy was 52.3 ± 7.6 year-old (range 40-70 year-old), while the mean age of those treated with inhaled B2 agonist alone or with leukotriens receptor antagonist was 49.3 ± 8.04 year-old and 45.1 ± 4.5 year-old, respectively. Twenty out of 32 patients (62.5 of those not treated with inhaled corticosteroid therapy) with either B2 agonist alone or with leukotriens receptor antagonist were in their fifth decade of life (40-49 year-old). In the other hand, 24 out of 60 patients (40%) treated with inhaled corticosteroid were in the same age group (fifth decade of life). Table-6 and figure-8 show patients distribution according to their age and type of the used therapy.

Table-6: patients' distribution according to their age and the type of the used therapy

	40-49 year-old		***50-59 year-old***		***60 years or older***	
	No.	***%***	***No.***	***%***	***No.***	***%***
Inhaled Corticosteriod	24	57.1%	23	67.6%	13	81.3%
B2 Agonist Inhaler	8	19.0%	9	26.5%	3	18.8%
B2 Agonist inhaler & Leukotreins	10	23.8%	2	5.9%	0	.0%
Total	42	100.0%	34	100.0%	16	100.0%

This study revealed that 5 out of 17 patients with evidence of acquiring myocardial infarction during the period of follow up (29.4%) had at least one marker of asthma severity, these include hospitalization for acute asthmatic attack, the need for systemic steroid to relieve severe asthmatic symptoms and/or the use of inhaled B agonist for the same purpose. Only 2 out of 18 patients with any marker of asthma severity had used low dose inhaled corticosteroid (11.1%), while the rest of them (16 patients, 88.9% of those with any marker of severity) were using other anti-asthmatic medications. Statistical analysis revealed that there was statistically significant association between the presence of any marker of severity and the development of acute myocardial infarction ($X2= 3.82$, p value < 0.05). Furthermore, Application of Chi square test showed that the use of low dose inhaled corticosteroid is associated with less frequency of having markers of asthma severity ($X2 = 4.32$, p value < 0.05). Table-7 and Table-8 show the frequency

distribution of the sample according to the presence of asthma severity markers and frequency of having MI and the type of the used therapy, respectively.

Table-7: Patients' distribution according to the presence or absence of any severity markers and the development of MI during the period of follow up.

	Myocardial Infarction		***No Evidence***		***Total***	
	No.	***%***	***No.***	***%***	***No.***	***%***
Any marker of severity	5	29.4%	13	17.3%	18	19.6%
No marker of severity	12	70.6%	62	82.7%	74	80.4%
Total	***17***	***100.0%***	***75***	***100.0%***	***92***	***100.0%***

Discussion:

It is widely recognized that asthma patients are at increased risk of adverse cardiovascular events for variable reasons [(16)]. One of the most important factors which had been recognized to play a major role in this higher risk of Coronary heart disease in asthmatic patients is the role of inflammation in the pathogenesis of atherothrombosis[(23-25)]. It had been hypothesized by many studies that there is at least a possible link between asthma and coronary heart disease depending on the fact of the role of chronic inflammatory nature of asthma[(26-27)]. This study revealed that out of 92 asthmatic patients, seventeen patients (18.5% of the sample) had evidence of myocardial infarction during the period of follow up(one year). In a study done by Iribarren et al at 2004, they found that the frequency of MI in asthmatic patient ranged from 12.8-17.3% of their sample depending on the factor under study[(27)]. These frequencies are quite similar to what we found in This study. At the same time, this frequency states that MI in asthmatic patients is much more frequent than its frequency among patients with previous history of unstable angina which had been estimated to be around 12%, taking into consideration that this percentage includes also those with other high risk factors for ischemic or coronary heart disease[(28)].

This study had revealed that there was a statistically significant difference in the frequency of MI in asthmatic patients depending on the type of the used therapy, with the highest frequency being observed in patients treated with anti-asthmatic medications rather than low dose inhaled corticosteroid therapy. This study demonstrated that 12 out of 17 patients with evidence of myocardial infarction was treated with short acting B2 agonist with or without leukotrien receptor antagonist, compared to the finding that 5 our of 60 patients (8.3%) treated with low dose inhaled corticosteroid had evidence of myocardial infarction. Suissa et al, found that inhaled corticosteroid use is associated with a decrease in the risk of myocardial infarction in patients with asthma and their finding suggested that that regular use of inhaled corticosteroids in patients with asthma reduces the risk of myocardial infarction by 50%[(16)]. Low dose inhaled corticosteroid had been shown to not only affect the frequency of MI or adverse cardiac events but its use had been shown to be associated with reduced risk of death in asthmatic patients[(29)]. Blais et al found in their study that the use of low dose inhaled corticosteroids was associated with decreased hospital admission of asthmatic patients regardless the cause of this admission, the effect of inhaled corticosteroids had been shown to be increased with the duration of therapy. It was 24 admissions, 1-15 days after the initiation of the inhaled corticosteroids compared to only 3 admissions after 13-24 months from the initiation of the inhaled corticosteroids therapy[(30)]. Although we found that anti-asthma medications were associated with higher frequency of MI in asthmatic patients compared to those who used low dose inhaled corticosteroids therapy, but some studies showed that the use of these medications rather than the low dose inhaled

corticosteroids, particularly the inhaled B2 agonists does not appear to increase the risk of fatal or non fatal acute myocardial infarction[31]. However, the study done by Suissa S et al had studied the effect of the B2 agonist therapy on patients with chronic obstructive pulmonary disease not on asthmatic patients.

It had been revealed by this study that 9 out of 60 female patients (15% of the female patients) had evidence of developing MI during the period of follow up, compared to 8 out of 23 male patients (34.8% of the male patients) had the same evidences. This higher frequency is in concordance with the results of Suissa et a study which showed that 75% of those asthmatics with MI were male patients[16]. But our study showed a little bit less frequency of MI among male population (34.8% versus 75%) when comparing our results with the similar study of Suissa et al. This is possibly because of our small sample size particularly in regard to the male distribution of the studied sample. Furthermore, regarding the age and gender distribution of our sample, 37 out of 69 female patients were in their 50s or older (53.6% of the female patients) i.e. they were in their peri or postmenapausal period which is associated with higher risk among female population[28]. This finding can explain the frequency of acute myocardial infarction among male patients in our study compared to Suissa et al study. in contrast, Iribarren C et al found in their study that asthma was independently associated with a modest but statistically significant increased hazard of coronary heart disease among women, but they did not studied the effect of inhaled corticosteroid therapy on this hazardous effect, particularly when we consider that in our study 50 out of 69 female patients (72.5%) used low dose inhaled corticosteroid in a frequency shown to be of a statistically significant difference. Even this higher frequency of use of low dose inhaled corticosteroid among female patients compared with the frequency of using low dose inhaled corticosteroids among male patients, can explain the significantly higher frequency of MI among male population (50 out of 60 patients treated with low dose inhaled corticosteroid (83.3% of those treated with low dose inhaled corticosteroid) were female).

Regarding the relationship between the severity of asthma and the development of MI, This study revealed that having any marker of sever asthma is associated with increasing frequency of acute myocardial infarction with 5 out of 18 patients with any severity marker (27.8%) having acute myocardial infarction during the period of follow up. It had been shown that the frequency of myocardial infarction were modestly less in patients with no marker of asthma severity, with only 12 out of 62 patients with no marker of severity (19.3%) having evidence of MI during the period of follow up. These findings are consistent with the finding of Suissa et al study, they found that the frequency of acquiring myocardial infarction among asthmatic patients with severe asthma was 21%[16]. Furthermore, analysis of our results indicated that patients who had used low dose inhaled corticosteroids, had lower frequency of asthma severity markers with statistically significant difference in this frequency compared with those who used other kinds of therapy. Only 2 out of 60 patients using low dose inhaled corticosteroid (3.3%) had markers of severe asthma. The rest of the 18 patients with severity markers were using other types of therapy. It is important to consider that if we exclude those patients with markers of severity from the sample of our study, this will further reduce the frequency of myocardial infarction among patients who used low dose inhaled corticosteroids in comparison with those using other kinds of therapy. It had been concluded from the study of Suissa et al that the risk of developing myocardial infarction was 81% lower with the use of low dose inhaled corticosteroids[16].

Conclusions:

The use of low dose inhaled corticosteroid was associated with decreased frequency of acute myocardial infarction in asthmatic patients initially diagnosed to have unstable angina in comparison to the frequency of MI among patients treated with other anti-asthmatic medications.

The risk of MI in male patients was higher compared with the same risk in female patients.

MI was more frequent among younger asthmatic patients.

Having any marker of asthma severity is associated with higher risk of having myocardial infarction.

Use of low dose inhaled corticosteroid is associated with less severe asthma .

We recommend a larger study with larger sample to confirm these findings.

Low dose of inhaled corticosteroid must be encouraged to be used and educate our patients about the beneficial effect in reducing the incidence of MI.

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