PREVALENCE AND ASSOCIATED FACTORS OF ASPIRIN NON-RESPONSIVENESS IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION IN DUHOK-IRAQ

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ABSTRACT

Background: The anti-platelets action of aspirin is not universal in all patients undergoing percutaneous coronary intervention (PCI). We evaluated the prevalence and associated risk factors of aspirin nonresponsiveness in patients undergoing stenting in Duhok-Iraq.

Methods: Eighty patients with coronary artery disease (CAD) undergoing PCI with drug eluting stents from 2015 to 2017 in Duhok-Iraq were enrolled after completion of the first year of dual antiplatelet (Aspirin plus Clopidogrel) while receiving aspirin 100 milligrams regularly. A detailed cardiac assessment, cardiovascular risk factors, and coronary angiographic profile of cases were reviewed. Aspirin responsiveness was assessed by measuring serum thromboxane B2 assay. Then a correlation with associated factors was performed. For major adverse cardiac events, responders and non-responders were followed up for a further two years.

Results: The mean age of cases was (59.28± 8.43 years). Thirty-nine were females. The aspirin nonresponsiveness was 14%. None of the risk factors were associated significantly with non responsiveness ($p>0.05$). Besides, significant differences in rates of adverse cardiac events were absent between responders and non-responders throughout the follow-up period.

Conclusions: Aspirin nonresponsiveness is not uncommon among our patients. No clear association with risk factors was detected. Short term adverse cardiac events rate between responder and non-responders was not affected.

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Keywords: Aspirin responsiveness, Aspirin resistance, Iraq

Aspirin is a cornerstone in the prevention of thrombo-embolic vascular events. It showed, based on evidences a clear reduction in major adverse cardiovascular events (MACE) in percutaneous coronary intervention (PCI) patients[1]. However, its action on prevention of platelets aggregation is not guaranteed in all patients. Worldwide 5.5%–60% of the population do not respond adequately to aspirin and this wide range of nonresponsiveness is related mainly to the lack of standardized aspirin responsiveness test[1,2]. Aspirin irreversibly inhibits cyclooxygenase-1 and reduces thromboxane A2 (TXA2) production. TXA2 is rapidly hydrolyzed to thromboxane B2 (TXB2). Urinary TXA2 metabolites are not specific because up to 30% of it are derived from extra-platelet sources, whereas serum TXB2 is derived only from platelet TXA2[2,3]. The Light transmission aggregometry (LTA) is the historical gold standard test for aspirin response, but there is a lack of standardization and is highly operator dependent. The TXB2 is more specific measure of the pharmacological effect of aspirin on platelets[2-4]. The main objective of this study is to assess the prevalence and

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associated risk factors of aspirin non responsiveness (ANR) in CAD patients undergoing PCI and the impact of ANR on the development of MACE by using the TXB2 test in Duhok-Iraq.

METHODS AND MATERIALS

Eighty patients with CAD who underwent PCI from 2015 to 2017 in Duhok Heart Center, Kurdistan, Iraq were enrolled. The ages of cases ranged between 40 and 80 years (59.28± 8.43) and included 41 males and 39 females. A detailed cardiac assessment of cases, CVS risk factors, and their coronary angiographic profile were reviewed. The main traditional cardiovascular risk factors, namely smoking, hypertension, diabetic mellitus, body mass index (BMI), family history of CAD, history of chronic kidney disease and dyslipidemia were recorded. The definition of above CVS risk factors depends on standardized definitions[5-9]. All patients also had their left ventricular ejection fraction measurement using two-dimensional echocardiography prior to PCI. Medications including beta-blockers, statins and proton pump inhibitors were registered.

All cases were taking aspirin (100mg) regularly after fisrt year post PCI underwent assessment of their serum TXB2 to evaluate aspirin responsiveness by thromboxane B2 ELISA Kit (Cayman chemical, Ann Arbor, MI, USA). a correlation with associated risk factors was undertaken. Follow up with median of 36 months of both responders and non-responders cases to aspirin for development of MACEs (non-fatal myocardial infarction, stent thrombosis, target vessel revascularization, cardiac death and ischemic stroke) throughout 2015-2019 was done. The research was approved by the ethics committee at the college of medicine, university of Duhok, Iraq and informed consents were obtained from all participants.

Statistical analysis: Data were evaluated using SPSS software (25:00, IBM, Chicago, IL, USA). Variables were categorized by the frequencies and percentages. Logistic regression was used for multivariate analysis to assess the effect of demographics and CVS risk factors to aspirin responsiveness. The Cox proportional-hazards regression with MACE as the end point in relation with demographics, CVS risk factors and aspirin resistance were performed. Kaplan-Meier survival curve for the end point of MACE, with comparison of survival curves (Log rank test) for patients with and without aspirin resistance was graphed. The $P<0.05$ was considered significant.

RESULTS

Table 1 showed baseline characteristics of enrollees. It showed that 14% of cases were non responders to aspirin. CVS risk factors were clustered among cases. Almost all cases were receiving beta-blockers and statins. More than half of cases had ≥ 2 coronary vessels disease and initially diagnosed with ACS.

Table 2, showed associations of demographics and CVS risk factors with aspirin non responsiveness and it showed none of the factors associated in logistic regression with aspirin non responsiveness.

Table 3, showed the effect of demographics, CVS risk factors and Aspirin non responsiveness on the occurrence of MACEs among all cases and when taking in regression models none of

the covariate showed significant associations with MACEs.

Table 1: Baseline characteristics

Characteristics	Category	No.	(%)
Age (years)	40 – 49	10	(12.5)
	50 – 59	31	(38.8)
	60 – 69	31	(38.8)
	70 – 80	8	(10)
Sex	Male	41	(51)
	Female	39	(49)
Initial diagnosis	ACS*	61	(76.2)
	Stable angina	19	(23.8)
Aspirin non	Yes	11	(14)
responsiveness (ANR)	No	69	(86)
Smoking	Yes	31	(38.8)
Diabetes	Yes	34	(42.5)
Hypertension	Yes	38	(47.5)
Dyslipidemia	Yes	38	(47.5)
Family history	Yes	8	(10)
Heart failure	Yes	21	(26.3)
Renal impairment	Yes	19	(23.8)
BMI (kg/m$^{2)}$	18 – 24	29	(36.3)
	25 – 29	36	(45)
	30 – 39	15	(18.8)
> One-vessel-disease	Yes	37	(46.3)
Proton pump inhibitors	Yes	20	(25)
Beta blockers	Yes	72	(90.0)
Statins	Yes	78	(97.5)
Total cases		80	(100)

***ACS= acute coronary syndrome.**

Table 2: Logistic regression of demographic and clinical factors on aspirin non responsiveness

Variable	b*	SE**	Wald	*P*	Exp(b)†	95% CI of Exp(b)
Age groups	-1.25693	0.73678	2.9104	0.0880	0.2845	0.0671 to 1.2058
Sex	0.36400	1.15137	0.09995	0.7519	1.4391	0.1507 to 13.7450
Diagnosis	0.069234	1.09862	0.003971	0.9498	1.0717	0.1244 to 9.2306
BMI groups	0.16701	0.62435	0.07156	0.7891	1.1818	0.3476 to 4.0178
Diabetes	-0.81260	1.22900	0.4372	0.5085	0.4437	0.0399 to 4.9345
Hypertension	0.047096	0.87096	0.002924	0.9569	1.0482	0.1901 to 5.7787
Heart failure	2.34156	1.25594	3.4760	0.0623	10.3974	0.8869 to 121.8987
Dyslipidemia	0.94474	1.27552	0.5486	0.4589	2.5721	0.2111 to 31.3359
Renal impair.	1.74479	1.24487	1.9644	0.1610	5.7247	0.4990 to 65.6765
>1 vessel disease	0.53366	0.96036	0.3088	0.5784	1.7052	0.2596 to 11.2006
Smoking	1.75017	1.08350	2.6092	0.1062	5.7556	0.6883 to 48.1264
Family history	0.33762	1.39859	0.05828	0.8092	1.4016	0.0904 to 21.7334
PPI	-0.60291	1.07747	0.3131	0.5758	0.5472	0.0662 to 4.5219
Betablockers	-0.41266	1.73482	0.05658	0.8120	0.6619	0.0221 to 19.8378
Statins	19.02628	7414.643	0.0000066	0.9980	1.7401	0.2488 to 13.2113

* Coefficients, **Standard Errors, † Odds ratio.

Table 3: Cox proportional-hazards regression with MACE as the end point

Covariate	b*	SE**	Wald	*P*	Exp(b)†	95% CI of Exp(b)
Aspirin resist.	0.2549	1.1481	0.04930	0.8243	1.2904	0.1360 to 12.2473
Age groups	0.1877	0.6785	0.07651	0.7821	1.2065	0.3191 to 4.5614
Sex	0.7929	1.3502	0.3449	0.5570	2.2098	0.1567 to 31.1672
Diagnosis	-1.7578	1.3167	1.7823	0.1819	0.1724	0.0131 to 2.2770
>I vessel disease	-0.9299	0.9576	0.9430	0.3315	0.3946	0.0604 to 2.5779
BMI groups	0.5721	0.4918	1.3536	0.2446	1.7721	0.6759 to 4.6460
Diabetes	0.9854	1.0013	0.9685	0.3251	2.6788	0.3764 to 19.0642
Heart failure	-0.5371	1.1962	0.2016	0.6534	0.5844	0.0560 to 6.0947
Hypertension	1.1515	0.8392	1.8827	0.1700	3.1628	0.6106 to 16.3833
Renal impair.	-0.3011	0.9464	0.1012	0.7503	0.7400	0.1158 to 4.7291
Smoking	0.6203	1.2784	0.2355	0.6275	1.8596	0.1518 to 22.7814
Dyslipidemia	1.2794	1.0237	1.5618	0.2114	3.5944	0.4833 to 26.7331

*** Coefficients, **Standard Errors, † Hazard ratio.**

Figure 1, Kaplan-Meier survival curve for the end point of MACE, with comparison of survival curves (Log rank test) for patients with and without aspirin non responsiveness. It showed no significant difference in the rate of MACE throughout the follow up period between the two groups.

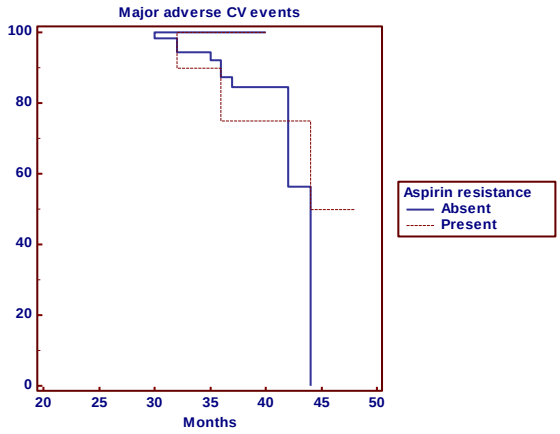

Figure 1: Kaplan-Meier survival curve for the end point of MACE.

DISCUSSION

To our best knowledge, this study is the first attempt in Iraq to determine the prevalence of aspirin non responsiveness in CAD cases undergoing percutaneous coronary intervention (PCI). It firstly showed that 14% of these cases were non responsive to aspirin. The study did not find any specific association between CVS risk factors and the rate of aspirin nonresponsiveness (ANR). It thirdly presented that the rate of MACEs was not affected significantly by ANR.

While there is a lack of a standardized test for aspirin responsiveness worldwide, the TXB2 test, used in the present study, is more specific than other existing tests. Serum TXB2 is a direct measure of the capacity of platelets to synthesize TXA2 and a specific measure of the pharmacological effect of aspirin on platelets[4]. The rate of aspirin resistance or ANR in this study was 14% in PCI patients. A study by Sadiq shows that the rate was 41% of both non and semi responders in some developing countries, such as India, a much higher rate than the one presented in the current study. By and large, when a combination of laboratory tests was used to define resistance (Verify now-aspirin, Optical aggregometry, and PFA-100), a lower rate (2%) was reported in comparison to using tests in isolation[10,11,12].

There are many genetic and non-genetic etiologies for ANR. In clinical practice, however, compliance as a possible causative factor should be kept in mind. This study did not demonstrate any clear demographic, clinic, and pharmacological parameters that were directly related to aspirin resistance. Christains et al. 2008, testing the relation of laboratory parameters with aspirin resistance, made the same conclusion. Some other studies found that only the female had a poor responsiveness. As for the age, Gum et al. 2001, found higher rates of ANR in older patients[13,14].

The current study did not find any association between ANR and MACEs in PCI patients. The risk between the responders and non-responders was similar in both stable angina and acute coronary syndrome. Pumuchic et al. 2006 also did not find any relation between MACEs and ANR in cases of stable angina; however, they reported a positive relation between ANR and ACS cases. Similar to other studies, this study also found that the cardiac death and survival were not affected in ANR and the Kaplan Meier curves were no separated significantly[15-17].

The clinical implication of (ANR) is also controversial. While a group of studies and analyses found an association between (ANR) and higher incidence of ischemic events including, myocardial infarction and stroke, another group of studies did not find this association. Neither a clear consensus on the association of aspirin resistance or ANR with CVS ischemic events exists in the medical literature. The findings of the present study cannot accordingly be generalized[18,19].

Regardless of what conclusions studies drive, a few concerns related to (ANR) should be addressed in the field of cardiovascular medicine. The first one is how to overcome the phenomenon of resistance, including a shift to alternatives such as clopidogrel. However, the rate of nonresponsiveness to clopidogrel is higher than aspirin itself in our area[20]. The second point relates with finding the most suitable test to measure aspirin response in PCI patients with a consideration that these patients are using multiple medications which could interact with aspirin action and erroneously affect the test result. Regardless of its pilot design, the present study is the first attempt in our region that examines this controversial topic in patients with coronary artery disease undergoing PCI and using the TXB2 assay[21, 22].

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پوختە

(ڕێژ ە وخوکارێن گرێدایی هە ستیارنەبوونا ئەسپرین ی ل جەم ئەنجامدەرێن تورین ڕەهیێن تانجی ل عیراق ی)

پێشەکی

کارتێکرنا دەرمانی ئەسبرینی ل جەم نەخوشیین ئەنجامدەرین تورین ڕەهیین تانجا دلی نە وەك هەڤن. ئەف ڤەکولینە بو زانینا ڕێژە وخوکارین گرێدایی هە ستیارنەبوونا ئەسپرین ی ل جەم ئەنجامدەرێن تورێن ڕەهیین تانجی ل عیراقێ هاتیە ئەنجام دان.

شێواز و نەخوش

هەشتی نەخوشیین ڕەها تانجا دلی ئەوین نشتەکەریا تورین ڕەها تانجا دلی بو هاتیە ئەنجامدان ل 2015–2017 ل سەنتەری ئازادی ی دلی ل دهوك ی هاتنە وەرکرتن بو فی ڤەکولینی . هە می نەخوشا دەرمانی ئەسبرین وەردکرت. جیروکا نەخوشیی و ئەنجامین ئەنجیوکرافیا ڕەهیین دلی وهوکارین مەترسیدار هاتنە ڤەکولین. باشان بو هەمی نەخوشا بشکنینا سرومبوکسان هاتە ئەنجامدان ز بو زانینا هەستیاریا دەرمانی ئەسبرین ی. و ل دویف دا کارتیکرنا هستیاریی ل سەر باری نەخوشان هاتە شروڤەکرن.

دەرئەنجام

ژیێ نەخوشان 59.28 سال بوون. 14٪ ژ نەخوشان دەرمانێ ئەسبرین نە یێ هەستیاربوو. چ خوکارین بەرجاف نەبوون بو نە هستیاریی. کارتێکرن لسەر دوارۆژا نەخوشا نەبوو د ماوێ دوو سالان دا.

دەرکەفتن

نە هستیاریا ئەسپرین ی یا بەربەلاڤە. لێ کارتێکرن لسەر بارێ نەخوشان نە یادیارە.

الخلاصة

مدى الانتشار والعوامل المرتبطة بعدم الاستجابة لدواء الاسبرين لدى مرضى التداخل القسطاري في العراق

خلفية البحث

إن تأثير الاسبرين ليس متجانساً في كافة المرضى الذين يأخذونه. هذه الدراسة تهدف الى معرفة مدى الانتشار والعوامل المرتبطة بعدم الاستجابة لدواء الاسبرين لدى مرضى التداخل القسطاري في العراق.

المرضى وطرق البحث

أجريت هذه الدراسة على ثمانين مريضاً مصاباً بمرض الشرايين التاجية والذين خضعوا لعملية الشبكة والبالون في مركز دهوك لأمراض القلب بين فترة 2015–2017 والذين يأخذون دواء الاسبرين (100 ملغم) باستمرار. وقد تحرت الدراسة عن التاريخ المرضي ونتائج القسطرة وعوامل الخطورة لدى كافة المرضى. وبعدها تم إجراء فحص مدى الاستجابة للاسبرين عن طريق فحص السرومبوكسان لكافة المرضى. ومن ثم تمت دراسة علاقة استجابة الاسبرين بعوامل الخطورة وعلى تطور المرض لمدة سنتين متتاليين لدى المرضى.

النتائج

معدل عمر المرضى هو (59.28 سنة). كما إن نسبة عدم الاستجابة للاسبرين هي (14%). ولم تجد الدراسة عاملاً محدداً له علاقة مع عدم الاستجابة بشكل مباشر. وفي نفس الوقت إن تاثير عدم الاستجابة غير واضحاً في المدى القريب على تطور المرض.

الاستنتاجات

إن نسبة عدم الاستجابة للاسبرين لدى مرضى التداخل القسطاري غير قليلة ولكن من دون تأثيرات ملموسة في المستقبل القريب على تطور المرض ومضاعفاته.