ORIGINAL ARTICLE

Factors Associated with Refusal of Reperfusion Therapy in Stemi patients

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ABSTRACT

Background: Despite significant advances in the management of patients with ST-segment elevation myocardial infarction, the issues of reperfusion therapy and its effectiveness are still extremely important, despite the large number of positive results of studies on its use. Unfortunately, it is still quite common in small hospitals and in the prehospital stage that medical workers refuse to carry out reperfusion therapy without sufficient justification.
Aim: To assess the reasons for refusing reperfusion therapy in STEMI patients admitted to the primary vascular unit (PVU) or a regional vascular center (RVC) to optimize management tactics.
Methods: The study was prospective, open, non-randomized. The study included all patients and STEMI from the 1st to the 16th of each month throughout 2018. A total of 848 patients were included. Observation of the surveyed persons and collection of endpoints continued for 18 months.
Results: Regression analysis showed that nitrate intake (OR 0.661, 95% CI 0.402-0.995) in patients was associated with any type of reperfusion, the presence in patients with chronic heart failure (CHF) and chronic kidney disease (CKD) were associated with rejection from reperfusion therapy. It should be noted that if the patient lived outside the regional center, the chances of receiving adequate reperfusion decreased (OR 2.911, 95% CI 2.006-4.222). Duration of symptoms longer than 12 hours also reduced the chances of reperfusion therapy. The presence of arterial hypertension (OR 1.860 95% CI 1.495-2.041, p = 0.034) and / or CHF (OR 1.522 95% CI 1.201-2.347, p = 0.047) was a factor that led to the refusal of reperfusion therapy in patients with STEMI living outside the regional center.
Conclusion: The characteristic features associated with the refusal of reperfusion were identified. This was chronic heart failure, chronic kidney disease and living outside the regional center, which significantly reduced the chances of receiving this type of therapy. An expected duration of STEMI symptoms of more than 12 hours was associated with refusal.
Keywords: Reperfusion therapy, STEMI, myocardial infarction

INTRODUCTION

In the world, according to the World Health Organization (WHO), about 7,000,000 myocardial infarctions (MI) occur annually[1]. At the same time, by 2030, their number is expected to increase to more than 9,000,000[2]. About 80% of all deaths associated with MI occur in countries with low and middle economic development[2]. A study in Minnesota (USA) showed that the incidence of MI from 1976 to 2006 decreased by 20%. It should be noted that one of the criteria for MI was an increase in MB-CK. However, this enzyme is less sensitive than troponins and does not detect about 25% of MI[3].

The large population-based ARIC study, which included about 360,000 people aged 35-74, also evaluated patients with possible and definite MI. Between 1987 and 1996, 14,942 such patients were hospitalized. It was found that during the observation period there was an insignificant trend towards an increase in the incidence of MI in men and women by 4.1% and 3.9%, respectively[4]. The frequency of recurrent myocardial infarctions over 9 years, on the contrary, decreased by 1.9% and 2.1% in this sex. In addition, the incidence of fatal MI decreased by 6.1% and 6.2%, respectively. Among the trends of the study, the authors note an increase in the median age of MI patients and an increase in the proportion of people with diabetes mellitus and arterial hypertension, as well as no change in mortality in the long term[4,5].

Creation of a system of medical care for patients with myocardial infarction, in other words, an "infarction" network, can reduce mortality from it to 4-7%[6]. However, there are a number of other important points that can "slow down" its positive dynamics. These are the features of patient transportation, the possibility of transferring the ECG to an expert (remote) center, sufficient qualification of medical personnel at all stages of medical care, modern equipment, groundless refusal to conduct reperfusion therapy, etc.

The analysis of medical care defects and missed diagnoses of cardiovascular diseases (CVD) in outpatient practice was carried out by Quinn GR et al (2017). It was found that the error rate in the diagnosis of coronary artery disease / myocardial infarction can reach 39%. This figure is explained by the serious condition of the patient, long-term diagnosis, and, less often, incorrect clinical conclusions of medical workers[7].

Another important defect in patients with ST-segment elevation myocardial infarction (STEMI) is the large window from the primary medical contact to the balloon. The Lambert L study published in 2010 demonstrated a significant increase in the risk of adverse outcomes in individuals who did not receive reperfusion therapy on time[8].

In a study by Nascimento BR et al. (2019) showed that more than 30% of STEMI patients do not receive reperfusion therapy in countries with a low and middle level of economic development[9]. A study by Barbarash O. L. et

al (2012) demonstrated that the main factors associated with the refusal of reperfusion therapy are: advanced age, the severity of the disease, the missed therapeutic "window" and a history of myocardial infarction[10].

The issues of reperfusion therapy and its effectiveness in patients with STEMI are still extremely important, despite the large number of positive research results on its use. Unfortunately, it is still quite often in small hospitals and at the prehospital stage that medical workers refuse to carry out reperfusion therapy without sufficient reason.

The aim of our study was to assess the reasons for refusing reperfusion therapy in patients with STEMI hospitalized in the primary vascular unit (PVU) or regional vascular center (RVC) to optimize management tactics.

MATERIAL AND METHODS

The study was conducted on the basis of regional vascular centers and primary vascular departments of the Ryazan region. The study is prospective, open-label, non-randomized. The study included all patients and STEMI from the 1st to the 16th of each month throughout 2018. A total of 848 patients were included.

Inclusion criteria were: 1) age 18 years and older; 2) permanent residence in the city of Ryazan and the Ryazan region; 3) hospitalization for STEMI in the period from January 1, 2018 to December 30, 2018 in the primary vascular department or the regional vascular center of the Ryazan region from the 1st to the 16th day of each month. There were no exclusion criteria at this stage of the study.

Observation of the surveyed persons and collection of endpoints continued for 18 months. The present endpoints were obtained as of 01/10/2020, the median of follow-up was 20.8 [17.4; 23.6] months. The endpoints were considered death from any cause during the first day, during hospitalization, after 30 days, 12 and 18 months from the date of hospitalization.

When evaluating reperfusion therapy, the time from primary medical contact to the initiation of thrombolytic therapy (TLT) or percutaneous coronary intervention (PCI), the presence of ECG criteria for TLT, the possibility of transferring the patient within 90 minutes for primary PCI, the presence of contraindications to TLT / PCI, were assessed, filling in the TLT card, PCI procedures, records of the reasons for refusing reperfusion, the stage of TLT. The data were analyzed from the medical record of the inpatient and entered into an electronic database. In the absence of contraindications, impossibility of PCI and persistence of symptoms and signs of transmural ischemia (ST segment elevations on the ECG) in individual patients with STEMI (large myocardial zone at risk and / or hemodynamic instability) Thrombolytic therapy 12-24 hours after symptom onset was also considered. In addition, thrombolysis was considered the initial stage of patient management and STEMI therapy had to be completed with primary PCI.

The study was conducted in accordance with the standards of Good Clinical Practice, Good Epidemiological Practice, and Good Patient Registry Practice. This study was conducted in accordance with regulatory documents, which guaranteed the observance of patients' rights at every stage.

Statistical analysis was carried out using Microsoft Excel 365 and Statistica 18.0 software. Descriptive statistics are represented by mean values, standard deviation (M ± SD) and median with an interquartile range Me (Q25; Q75) for different types of distributions. The distribution of features was assessed using the Shapiro-Wilk, Lilliefors, Kolmogorov-Smirnov criteria. The p value for all of the listed criteria was more than 0.05, then the distribution of the studied trait was regarded as normal, if the value of any of these criteria was less than 0.05, then the distribution of the studied trait was regarded as different from normal. In the case of distribution of the values of the characteristic other than normal, the Mann-Whitney test was used. Comparison of two unrelated groups on a qualitative basis was carried out using the chi-square test (Pearson). Revealing the relationships of the studied features was carried out using correlation analysis with the calculation of the rank correlation coefficient. To build the models, we used multiple logistic regression with an assessment of significance and odds ratio (OR). The model was built on the basis of univariate regression analysis, factors that have significant associations with the onset phenomenon were included. In all cases, the differences were considered statistically significant at $p < 0.05$.

RESULTS

The analysis included 848 STEMI patients. The clinical characteristics of patients, depending on the type of reperfusion therapy are presented in table 1.

There were no differences in the groups by sex and age. Differences in the multivariate Kruskal-Wallis test in the reperfusion therapy groups were noted for the following characteristics: current smoking ($p = 0.001$), dyslipidemia ($p = 0.040$), CKD ($p = 0.001$), peripheral atherosclerosis ($p < 0.001$), atrial fibrillation ($p = 0.046$), CHF ($p = 0.032$), history of stroke ($p = 0.037$), average SBP ($p = 0.024$), heart failure classes during hospitalization ($p = 0.049$), RAAS blockers ($p = 0.044$), diuretics ($p = 0.039$), statins ($p = 0.014$) and nitrates ($p = 0.001$).

In order to assess the presence / absence of associations of various factors with the refusal of reperfusion therapy, a correlation analysis was carried out in the groups of people who received and did not receive it. Were selected factors that could influence the decision to refuse therapy. Further, a univariate analysis was carried out with an assessment of the odds ratio (Table 2)

The table shows that the intake of nitrates (OR 0.661, 95% CI 0.402-0.995) in patients was associated with any type of reperfusion. On the other hand, the presence of CKD and CHF in patients were associated with the refusal of reperfusion therapy. It should be noted that if the patient lived in the region, the chances of getting adequate reperfusion decreased (OR 2.911, 95% CI 2.006-4.222). Time also played a significant role in the decision to conduct this therapy. Moreover, the chances of receiving any type of reperfusion within 24 hours could be higher than in the first 12 hours (OR 0.031, 95% CI 0.019-0.050 versus OR 0.309, 95% CI 0.215-0.444, respectively, p

<0.01). Duration of symptoms longer than 12 hours reduced the chances of reperfusion therapy.

When assessing the effect of comorbidity on the decision on therapy, it was found that 2 comorbidities increased the likelihood of refusing to reperfusion (OR 1.479, 95% CI 1.007-2.173). Moreover, the presence of 3 or more diseases did not affect this decision in any way (OR 1.143, 95% CI 0.661-1.977).

When evaluating patients living outside the regional center, it was revealed that, in addition to the time factor, the decision to start reperfusion can be influenced by concomitant diseases and a lighter (Killip 1) clinical condition of the patient at the time of hospitalization. Nitrate intake before hospitalization was associated with the onset of reperfusion (Table 3).

Table 1: Main characteristics of STEMI patients depending on the type of reperfusion therapy

Sign	TLT (n=59)	PCI (n=464)	TLT+PCI (n=176)	Noreperfusion (n=149)	p
Average age, years (M±SD)	64,3±9,3	62,9±13,1	63,4±12,9	63,3±10,4	0,112
Malegender, (%)	65,0	63,8	65,0	64,4	0,373
Smoking, (%)	41,0	38,9	41,4	34,5	**0,001**
Arterialhypertension, (%)	49,0	52,0	41,1	50,0	0,091
Dyslipidemia, (%)	40,0	46,0	52,8	41,0	**0,040**
Diabetesmellitustype 2, (%)	15,6	17,0	17,4	17,0	0,243
CKD, (%)	1,8	1,5	0,5	4,7	**0,001**
Peripheralatherosclerosis(%)	0,0	2,0	8,1	3,0	**<0,001**
AF, (%)	2,0	3,0	11,5	5,8	**0,046**
Anemia, (%)	4,1	4,1	5,5	4,6	0,065
CHF (%)	20,0	16,5	15,7	25,5	**0,032**
Stroke, (%), (%)	6,9	5,4	12,9	7,5	**0,037**
MI, (%)	12,4	14,9	11,6	14,9	0,513
PCI, (%)	9,5	11,0	8,2	10,0	0,396
CABG, (%)	1,6	3,9	2,9	2,6	0,187
Clinicalstatusathospitalization					
SBP	124±4,8	129±4,8	130±4,8	127±4,8	**0,024**
DBP	74±4,8	77±4,8	73±4,8	75±4,8	0,282
Heart rate	78±4,8	77±4,8	80±4,8	79±4,8	0,394
Killip 1, (%)	55,0	61,0	40,9	54,0	**0,011**
Killip 2, (%)	26,7	22,0	37,8	28,0	**0,037**
Killip 3, (%)	11,0	9,8	12,6	10,6	**0,046**
Killip 4, (%)	7,7	3,7	17,3	7,9	**0,028**
Therapybeforehospitalization					
RAAS blockers, (%)	35,7	30,2	40,2	37,0	**0,044**
Beta-blockers, (%)	12,5	11,4	14,1	12,7	0,113
Diuretics, (%)	15,7	29,0	18,1	30,4	**0,039**
Calciumchannelblockers, (%)	9,8	11,1	8,3	10,8	0,298
Nitrates, (%)	12,9	8,9	51,3	14,0	**0,001**
Statins, (%)	29,4	30,0	25,8	40,9	**0,014**
Aspirin, (%)	23,6	24,9	25,1	25,1	0,857
P2Y12 receptor blockers (clopidogrel / ticagrelor), (%)	8,4	9,8	10,0	10,0	0,196
Placeofresidence					
Accommodation in the regional center, (%)	55,0	25,4	77,8	22,7	33,6
Accommodation outside the regional center, (%)	45,0	74,6	22,2	77,3	66,4
Time from symptom onset to reperfusion therapy					
0-12 hours, (%)	70,0	93,2	82,0	49,4	47,7
0-24 hours, (%)	72,0	96,1	100,0	36,7	72,0
Morethan 12 hours, (%)	30,0	6,8	18,0	51,1	52,3
Comorbidity (number of concomitant diseases)					
0, (%)	4,5	8,5	2,8	9,5	2,2
1, (%)	58,8	57,6	62,1	55,1	53,7
2, (%)	25,7	20,3	25,0	24,0	32,0
3ormore, (%)	11,0	13,6	10,1	11,4	12,1

Within the framework of this analysis, in people living outside the regional center, despite a small sample, a regression analysis was carried out, which revealed independent predictors of refusal from reperfusion therapy in patients (correction by gender, age):

• Hospitalization of patients after 12 hours after initiation of symptoms (OR 1.313 95% CI 1.049-1.753, p = 0.001)
• A history of CHF (OR 1.734 95% CI 1.112-2.048, p = 0.042)
• A history of hypertension (OR 1.781 95% CI 1.118-1.960, p = 0.017).

In order to level the time factor, an additional analysis was carried out with correction for gender, age, time factor, clinical status and number of NCDs. The following predictors of reperfusion therapy refusal were identified:
• A history of CHF (OR 1.522 95% CI 1.201-2.347, p=0.047)
• A history of hypertension (OR 1.860 95% CI 1.495-2.041, p=0.034).
Thus, the presence of hypertension and or CHF was a factor that led to the refusal of reperfusion therapy in STEMI patients living outside the regional center, which contradicts clinical guidelines.

Table 2: Associations of various factors with refusal of reperfusion therapy

Sign	OR	95% CI
Smoking, (%)	0,788	0,544-1,142
Arterialhypertension, (%)	1,041	0,731-1,481
Dyslipidemia, (%)	0,775	0,541-1,110
Diabetesmellitustype 2, (%)	0,983	0,612-1,577
CKD, (%)	2,822	1,092-7,294
Peripheralatherosclerosis, (%)	0,776	0,265-2,270
AF, (%)	1,220	0,573-2,594
Anemia, (%)	1,062	0,459-2,460
CHF (%)	1,557	1,027-2,360
Stroke, (%), (%)	0,992	0,504-1,950
MI, (%)	1,075	0,652-1,774
PCI, (%)	0,990	0,550-1,781
CABG, (%)	0,776	0,265-2,270
Killip 1, (%)	0,929	0,652-1,325
Killip 2, (%)	1,099	0,740-1,630
Killip 3, (%)	1,016	0,574-1,800
Killip 4, (%)	1,090	0,567-2,096
RAAS blockers, (%)	1,178	0,815-1,702
Beta-blockers, (%)	1,056	0,620-1,798
Diuretics, (%)	1,286	0,871-1,898
Calciumchannelblockers, (%)	1,048	0,591-1,858
Nitrates, (%)	0,661	0,402-0,995
Statins, (%)	1,560	1,084-2,245
Aspirin, (%)	0,997	0,662-1,501
P2Y12 receptor blockers (clopidogrel/ticagrelor)	1,039	0,576-1,873
Placeofresidence		
Accommodation in regional center(%)	0,344	0,237-0,498
Accommodation outside the regional center(%)	2,911	2,006-4,222
Time from symptom onset to reperfusion therapy		
0-12 hours, (%)	0,309	0,215-0,444
0-24 hours, (%)	0,031	0,019-0,050
Morethan 12 hours, (%)	3,240	2,252-4,662
Comorbidity (number of concomitant diseases)		
0, (%)	0,390	0,118-1,285
1, (%)	0,775	0,543-1,106
2, (%)	1,479	1,007-2,173
3ormore, (%)	1,143	0,661-1,977

Table 3. Associations of various factors with the decision to refuse reperfusion in STEMI patients living outside the regional center

Sign	OR	95% CI
Malegender	0,524	0,342-1,443
Smoking	1,790	1,086-2,950
Arterialhypertension	4,136	2,532-6,756
Dyslipidemia	1,847	1,143-2,984
Diabetesmellitustype 2	2,080	1,055-4,103
CKD	2,917	0,579-14,695
Peripheralatherosclerosis	0,563	0,121-2,615
AF	1,761	0,623-4,979
Anemia	2,456	0,733-8,232
CHF	2,080	1,107-3,909
Stroke	1,270	0,506-3,184
MI,	3,431	1,591-7,399
PCI	2,537	1,060-6,073
CABG	1,738	0,408-7,408
Killip 1	1,759	1,109-2,790
Killip 2	0,630	0,382-1,037
Killip 3	1,016	0,490-2,107
Killip 4	0,741	0,328-1,676
Regularmedicationbeforehospitalization		
RAAS blockers	1,014	0,630-1,632
Beta-blockers	1,037	0,525-2,047
Diuretics	1,550	0,928-2,558
Calciumchannelblockers	1,185	0,564-2,488
Nitrates	**0,384**	**0,206-0,713**
Statins	0,976	0,599-1,591
Aspirin	0,974	0,571-1,659
P2Y12 receptor blockers (clopidogrel / ticagrelor)	1,023	0,478-2,191
Time from symptom onset to reperfusion therapy		
0-12 hours	0,428	0,269-0,683
0-24 hours	0,245	0,151-0,397
Morethan 12 hours	**2,334**	**1,464-3,727**
Comorbidity (number of concomitant diseases)		
0	0,271	0,062-1,182
1	0,836	0,528-1,324
2	1,540	0,932-2,545
3ormore	1,082	0,534-2,194

DISCUSSION

Analyzing the frequency of various types of reperfusion therapy in STEMI patients, it should be noted that the data obtained in our study do not correspond to the target indicators. Thus, the frequency of primary PCI in STEMI should reach 90%, in the Ryazan region this figure was 44.7%. In general, if we take the percentage of people with STEMI who received reperfusion, it was quite high - 64.6%[11].

When assessing the groups depending on the type of reperfusion, differences were found in the frequency of smokers, in the level of dyslipidemia, the level of CKD, peripheral atherosclerosis, AF, CHF, and a history of stroke. At the same time, in the group of patients who did not receive reperfusion, there was a high incidence of CKD and CHF, which indicates a greater "severity" of these patients. However, if we analyze the risk factors, then the lowest smoking frequency is noted in this group. The primary PCI group had lower levels of risk factors, with the exception of smoking. It is interesting that the frequency of anemia and peripheral atherosclerosis in our study was significantly lower than in the RECORD-3 register [12,13]. Thus, STEMI patients had their own unique anamnestic characteristics that could influence the development of adverse outcomes.

The therapy of patients before hospitalization, depending on the type of reperfusion therapy, also had a number of features. Thus, BRAAS was most often used in the group of patients with TLT+PCI or without reperfusion therapy. Diuretics were more commonly used in the non-reperfusion group. Statin use was also higher in this group. An interesting fact is the high frequency of nitrate use in persons who received PCI + TLT. This indirectly indicates a high incidence of ischemic heart disease in this group before the development of present STEMI. It should be noted that according to other studies, the frequency of use of nitrates from pre-index STEMI in all groups of reperfusion therapy was significantly higher[12-14].

When assessing the clinical status, the lowest mean SBP levels were noted in the TLT group. When dividing patients according to the Killip-Kimball classification, there is a clearly lower incidence of severe patients in the group of primary PCI, which may have influenced the risk of adverse outcomes. The highest incidence of cardiogenic shock and pulmonary edema (Killip 3 and 4) was observed in the pharmacoinvasive approach group and reached 29.9% of patients. Studies in China, Europe and the United States show a high incidence of severe STEMI in the group of patients who did not receive reperfusion. However, in our study in this group there were 18.5% of persons with Killip 3 and 4[15-18].

Primary PCI was most often performed in residents of the regional center (77.8% versus 22.2% when living outside the regional center). In the group of patients without reperfusion therapy, the ratio of residents living in and outside the regional center differed from other strategies and amounted to 33.6% and 66.4%, respectively. These data indicate that the reperfusion refusal rate may be higher outside the regional center.

In terms of the number of comorbid diseases, the PCI and non-reperfusion groups should be noted, where there

was the smallest number of persons without concomitant pathology (2.8% and 2.2%, respectively). It is also noteworthy that the number of patients with two or more diseases in the group without reperfusion was 44.1%.

In order to assess the significance of factors in refusal of reperfusion, a univariate analysis was carried out, which demonstrated that taking nitrates and Killip 4 were associated with TLT, while taking diuretics (OR 2.047, 95% CI 1.260-3.327), the presence of CHF (OR 1,720, 95% CI 1,040-2,847) or CKD (OR 5,743, 95% CI 1,177-28,030) in history were associated with refusal from any type of reperfusion therapy. It was also revealed that living in the regional center is a factor associated with reperfusion therapy (OR 0.344, 95% CI 0.237-0.498). If the patient lived in the area, the chances of getting adequate reperfusion decreased (OR 2.911, 95% CI 2.006-4.222). It should be noted that time also played a significant role in the decision to conduct this therapy. At the same time, the chances of getting any type of reperfusion within 24 hours were higher than in the first 12 hours (OR 0.031, 95% CI 0.019-0.050 versus OR 0.309, 95% CI 0.215-0.444, respectively, p <0.01). Duration of symptoms longer than 12 hours reduced the chances of reperfusion therapy (OR 3.240, 95% CI 2.252-4.662).

Additional analysis comparing the chances of TLT and refusal of reperfusion showed that living in the regional center (OR 1.653, 95% CI 1.049-2.605), symptoms for more than 12 hours (OR 1.677, 95% CI 1.108-2.539), the presence of 2 or more comorbid diseases (OR 1.593, 95% CI 1.007-2.520) were associated with refusal from TLT (Table 17). Living outside the regional center (OR 0.605, 95% CI 0.384-0.953), symptoms up to 12 (OR 0.596, 95% CI 0.394-0.902) and up to 24 hours (OR 0.046, 95% CI 0.025-0.083), as well as the absence of comorbid pathologies (OR 0.199, 95% CI 0.058-0.677) were associated with a higher chance of TLT.

The data obtained indicate that, in general, patients with comorbid pathology, especially with CHF and CKD, including those taking diuretics, were less likely to receive reperfusion in general or TLT. These data are at variance with data from, for example, the ACACIA study, where factors associated with refusal from reperfusion therapy were: diabetes mellitus (OR 0.54, 95% CI 0.36-0.81, p <0.01) and pulmonary edema in hospitalization time (OR 0.34, 95% CI 0.17-0.70, p <0.01), etc [14].

Thus, patients living outside the regional center had, in general, less access to reperfusion therapy. At the same time, the presence of concomitant pathology, in contrast to other studies, significantly limited its use in clinical practice, which requires additional analysis. However, the initial reason for this result is an incorrect assessment of the risk of developing adverse events against the background of reperfusion therapy, which leads to its rejection. Additional training of medical workers is needed on indications and contraindications for TLT and primary PCI.

CONCLUSION

Thus, the characteristic features associated with the refusal of reperfusion were identified. This was, first of all, severe comorbidities (CHF and CKD, the presence of comorbidity, but no more than 2 diseases) and living outside the regional center, which also significantly reduced the chances of receiving this type of therapy. An expected duration of STEMI symptoms of more than 12 hours was associated with refusal. However, the chances of receiving TLT were higher if hospitalized within 24 hours, compared to 12 hours.

Limitations of the study: The lack of continuous inclusion of STEMI patients and the comparability of groups only by sex and age limits the use of a number of statistical methods in data analysis.

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