Management of Patients with Refractory Unstable Angina in a Hospital without Cardiac Surgery Department. Invasive or Conservative Treatment? TRUCS Study

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Introduction: We compared invasive (on-site coronary angioplasty or emergency air-ambulance transfer for bypass grafting) versus conservative (persistent medical treatment) strategies in the management of refractory unstable angina in geographically isolated hospitals without cardiac surgical facilities.

Methods: Of 719 patients presented with class IIIb (primary unstable angina) and IIIc (post-infarction angina) unstable angina from 1 March 1997 to 31 October 1998, 152 developed refractory symptoms (persistent or recurrent chest pain ± ECG changes after 48 hrs "optimal" medical therapy). One hundred and forty eight of these patients enrolled in this prospective randomised study (invasive strategy group: 76, conservative strategy group: 72) and were compared on an intention-to-treat basis.

Results: All invasively treated patients underwent coronary angiography, 40 of 76 (53%) underwent urgent coronary angioplasty, 19 of 76 (25%) were transferred by emergency air ambulance for bypass grafting surgery and 17 of 76 (22%) continued on medical treatment. Although all group B patients were intended to be treated medically, 27 out of 72 (38%) were managed invasively due to persistent refractory symptoms [coronary angiography: 27 (38%), coronary angioplasty: 23 (32%), bypass grafting surgery following emergency air transfer: 4 (6%)]. Outcomes (invasive vs conservative): *a) in-hospital:* stabilization (96% vs 43%, p=0.0001), non-fatal MI (2.6% vs 4.2%, p=NS), death (1.3% vs 8.3%, p=0.046) combined outcome (3.9% vs 12.5%, p=0.053) and hospitalization (11.4±6.3 vs 12.4±8.0 days, p=NS). *b) 30-days follow-up:* non-fatal MI (2.6% vs 4.2%, p=NS), death (2.6% vs 11.1%, p=0.030) and combined outcome (5.3% vs 15.3%, p=0.031). *c) 12 month follow-up*: non-fatal MI (3.9% vs 4.2%, p=NS), death (3.9% vs 12.5%, p=0.053), combined outcome (7.9% vs 16.7%, p=NS), readmissions for unstable angina: (17.1% vs 23.6%, p=NS), late PTCA: (15.8% vs 11.1%, p=NS) and c) late CABG: (7.9% vs 12.5%, p=NS).

Conclusion: Invasive treatment of patients with refractory angina in remote areas without surgical backup results in significant in-hospital stabilisation and reduction of in-hospital and at 30-days major events. Coronary angioplasty in stand-alone units and air-transfer of these patients seems safe. These findings suggest that invasive management of refractory unstable angina in isolated hospitals should be the treatment of choice.

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Although invasive treatment is advised for the management of refractory unstable angina[1], its use is often not an option due to the lack of suitable hospital facilities (less than 10% of European hospitals are equipped with coronary angioplasty facilities and even less have on-site cardiac surgery back-up)[2].

In hospitals without on-site cardiac surgery, the treatment of unstable angina is limited to one of the following strategies: 1) persistence in pharmaceutical treatment, 2) diagnostic on-site catheterization and urgent transfer in hospital with cardiac surgery unit for further management, 3) transfer in hospitals with cardiac

surgery back-up for diagnostic catheterization and possibly revascularization or 4) on-site invasive management in cases where angioplasty is considered feasible and urgent transfer of patients with need for coronary artery bypass grafting in cardiac surgery center.

The transfer of patients with unstable angina usually does not present important problems in geographically non-isolated areas [3] and consequently the second and the third above mentioned strategies may be preferable in such areas. In geographically isolated areas, however, transfer is questionable and sometimes not possible. Thus, either persistence in pharmaceutical treatment or invasive revascularization from experienced personnel in individual units of angioplasty could be the most attractive alternative approaches. Regarding the viability of such units, the need of surgical back-up during coronary angioplasty and the danger of transfer of unstable patients are critical. European data have shown that the need of urgent, cardio-surgical rescue intervention during angioplasty was 0.7% in 1994[4], while today it is estimated to be lower thanks to improved technology and increased use of intra-coronary stents[5]. In addition, diagnostic and therapeutic procedures in selected stable[6] and unstable patients[7-8] have been recently reported to be successful and safe in hospitals without on-site cardiac surgery back-up, while the results of primary angioplasty in small independent units were comparable to those of centers with on-site cardiac surgery facilities[9-12]. However, in patients with unstable angina, there are no references in literature regarding the safety of angioplasty in isolated hospitals without on-site cardiac surgery back-up. The aim of TRUCS (Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery) study was to compare the invasive (on-site angioplasty or emergency air-ambulance transfer for coronary bypass grafting) with the conservative (persistent pharmaceutical) treatment in the management of patients with refractory unstable angina in geographically isolated hospitals without cardiac surgery back-up.

Methods

Organization of the study

The TRUCS study was a randomised prospective study that compared invasive versus conservative treatment, on an "intention-to-treat" based analysis. The study was performed in North-Western Greece and both the two existing General Regional Hospitals participated. The two hospitals cover a population of 380,000 residents. During the period that the cardio-surgical study took place, there was no cardiac surgery unit in none of the hospitals. The area is geographically isolated (480 kilometers, 6 hours driving duration and one hour by air transportation to the nearest cardiac surgery center). Patients started enrolling in the TRUCS study on 1 March 1997, following protocol approval by the Scientific Committees of the two participating hospitals. The enrollment of patients ended on 31 October 1998.

Eligibility of patients

Eligible patients were those who were admitted to the coronary care unit with class IIIb (primary unstable angina) and IIIc (post-infarction angina) unstable angina and subsequently developed refractory unstable angina, without development of new myocardial infarction or death within the first 48 hours after their admission. Refractory unstable angina was determined as recurrent symptoms 48 hours after the beginning of treatment (typical chest pain of more than five minutes duration with or without electrocardiographic changes) despite "optimal" pharmaceutical treatment or as chest pain recurrence with or without ECG changes during hospitalization. Patients who refused to give their informed consent were excluded.

Randomization

After their informed consent to participate in the study, eligible patients were randomized to either group A (invasive treatment) or group B (conservative treatment).

Treatment

All patients admitted to coronary care units with class IIIb and IIIc unstable angina were treated for 48 hours with aspirin, unfractioned or low molecular weight heparin (choice of attending doctor), intravenous infusion of nitrates, calcium antagonists and b-blockers, unless a contraindication existed. Angiotensin converting enzyme inhibitors and aggressive anti-diabetic treatment were administered according to current guidelines. Aggressive treatment of lipid reduction usually began 48 hours after the patients

transfer to the clinic. Patients that remained symptomatic after 48 hours of anti-angina treatment were characterized as having refractory unstable angina.

Group A patients (invasive treatment)

All patients of group A (invasive treatment) underwent on-site coronary angiography, on the day of refractory unstable angina diagnosis. Following coronary angiography, revascularization intervention was performed (i.e. on-site angioplasty or coronary artery bypass grafting in the nearest on-duty cardiac surgery center after air-ambulance transfer). Revascularization was recommended in all patients with a minimum of 70% diameter occlusion of any artery which vascularized a significant percentage of the myocardium. Percutaneous coronary intervention was recommended in cases where one or two significant stenoses existed and coronary artery bypass grafting was preferred in patients with three-vessel disease or left coronary artery stem disease (guidelines of ACC/AHA[13-14]). When necessary intravenous IIb/IIIa platelet inhibitors, intracoronary stents, and intraaortic balloon counterpulsation were used as ancillary treatment in coronary angioplasty.

Group B patients (conservative treatment)

All patients of group B (conservative treatment), unless a contraindication existed, continued their pharmaceutical treatment with the initial "optimal" therapeutic regimen and progressively increasing dose of nitrates and calcium antagonists. Patients that remained in refractory ischemic condition for five days, were treated invasively (identical to group A). These patients were considered as "unstable", irrespective of final outcome.

Follow-up

Following their discharge from the hospital, patients were re-examined one month later and then after twelve months in out-patient clinics.

Final endpoints

Primary endpoints were stabilization during hospitalization, major combined cardiac events (new non-fatal myocardial infarction and death) and duration of hospitalization. Secondary endpoints were readmission for unstable angina, need for late coronary angiography and late revascularization (angioplasty and coronary artery bypass grafting). Stabilization was determined as the condition that did not result in myocardial infarction or death during hospitalization. Moreover, group B patients were considered unstable if they needed coronary angiography due to refractory angina during hospitalization. Myocardial infarction was determined as the existence of two out of three conventional criteria-typical chest pain, diagnostic electrocardiogram (mainly new Q wave) or increase of biochemical markers of myocardial damage according to the following definitions. For myocardial infarction not related to intervention procedure: one measurement of CK-MB concentration higher than the hospital's diagnostic limit for myocardial infarction. For myocardial infarction related to percutaneous coronary intervention: one measurement of CK – MB, 1.5 times the hospital's diagnostic limit for myocardial infarction. Only the appearance of new Q waves was used for the diagnosis of myocardial infarctions related to coronary artery bypass grafting. Unstable angina was defined as the typical chest pain at rest or at small effort with or without electrocardiographic changes for which hospitalization was necessary. Duration of hospitalization was calculated from the day of admission to the day of discharge (including days of hospitalization after coronary artery bypass grafting). Late coronary angiography and revascularization intervention was defined as the one performed after hospital discharge.

Statistical analysis

The two groups were compared on the basis of the "intention to treat" analysis. All data were expressed as mean value ± standard deviation. Student (t-test) was used for comparison of mean quantitative variables while categories qualitative characteristics were compared using the Chi square method. Values of $p<0.05$ were considered statistically significant.

Results

Study population

During the study, 719 consecutive patients with class IIIb and IIIc unstable angina were enrolled. Out of the 719 patients, 152 developed refractory unstable angina. One hundred and forty eight patients (male: 108, mean age ± SD: 62.6±9.5 years old) were en-

Table 1. Baseline characteristics of the patients randomly assigned to invasive and conservative treatment.

	Group A - invasive strategy (N=76)	Group B - conservative strategy (N=72)	P value
Age – years	62±9	63±10	NS
Male Gender – no. (%)	57 (76)	51 (71)	NS
Risk Factors – no. (%)			
Current smoker	26 (34)	20 (28)	NS
Ex -smoker	12 (16)	10 (14)	NS
Hypertension	41 (54)	38 (53)	NS
High cholesterol level	40 (53)	40 (55)	NS
Diabetes mellitus	22 (29)	20 (28)	NS
Family history of CAD	24 (32)	21 (29)	NS
Coexisting illness – no. (%)			
PVD	12 (16)	10 (14)	NS
History of stroke	5 (7)	4 (6)	NS
Prior procedures– no. (%)			
Coronary angiography	29 (38)	28 (39)	NS
Coronary angioplasty	12 (16)	10 (14)	NS
CABG	10 (13)	8 (11)	NS
Unstable angina class on admission –no. (%) (Braunwald classification)			
Class IIIb	59 (78)	57 (79)	NS
Class IIIc	17 (22)	15 (21)	NS
Baseline left ventricular function – no (%) (echocardiographically assessed)			
Good	38 (50)	37 (51)	NS
Moderate	26 (34)	23 (32)	NS
Bad	12 (16)	12 (17)	NS

NS: non-statistically significant; CAD: coronary artery disease; PVD: peripheral vascular disease; CABG: coronary artery bypass graft surgery.

rolled in the study (invasive treatment: 76, conservative treatment: 72), while 4 patients out of the 152 refused to give their informed consent and were excluded. The baseline patient characteristics appear in table 1.

In-hospital management

The initial pharmaceutical management in the two groups was similar (Table 2). All patients of group A underwent coronary angiography, 40 out of 76 (53%) underwent urgent coronary angioplasty, 19 out of 76 (25%) were transfer with emergency air-ambulance for coronary artery bypass grafting and 17 out of 76 (22%) continued with pharmaceutical treatment (Table 2). Although the intention was to manage all patients of group B with pharmaceutical treatment, 27 of 72 (38%) were treated invasively due to recurrent symptoms [coronary angiography: 27 (38%), coronary angioplasty: 23 (32%), coronary artery bypass grafting after emergency air-ambulance transfer: 4 (6%)] (Table 2).

Use of IIb/IIIa platelet inhibitors, coronary stents and intraaortic balloon counterpulsation

IIb/IIIa platelet inhibitors were administered in 38/40 of (95%) patients of group A and in 22/23 (96%) patients of group B. Intracoronary stents were implanted in 33/40 (85%) patients of group A and 20/23 (85%) patients of group B, while intraaortic balloon counterpulsation was used in 3/40 (7.5%) patients of group A.

Endpoint analysis

Endpoint analysis is summarized in table 3. In-hospital stabilization in patients of group A and B was achieved in 73 out of 76 (96%) and 31 out of 72 (43%) patients respectively (p=0.0001). During ho-

Table 2. In-hospital management of the study population.

	Group A - invasive treatment (N=76)	Group B - conservative treatment (N=72)	P value
Initial medical treatment - no (%)			
Aspirin	71 (93)	65 (90)	NS
Unfractionated heparin IV	56 (76)	55 (76)	NS
Low molecular weight heparin	13 (17)	10 (14)	NS
Nitrates (IV)	76 (100)	72 (100)	NS
Beta-blocker	52 (68)	51 (71)	NS
Ca antagonist	51 (67)	50 (70)	NS
ACE inhibitor	19 (25)	17 (24)	NS
Statin	14 (18)	17 (24)	NS
Diuretic	6 (8)	6 (8)	NS
Digitalis	3 (4)	4 (6)	NS
Coronary angiography - no (%)	76 (100)	38 (53)	0.00001
Revascularisation - no (%)			
Coronary angioplasty	40 (53)	23 (32)	0.013
CABG	19 (25)	4 (6)	0.0011

NS: non-statistically significant; CABG: coronary artery bypass graft surgery.

spitalization, the combined percentage of major events in group A was 3.9% [3 major cardiac events (1 death and 2 non-fatal myocardial infarctions] versus 12.5% [9 major cardiac events (6 deaths and 3 no-fatal myocardial infarctions)] in group B (p= =0.053). At 30 days, the percentage of major events was substantially considerably less in the invasively managed group compared to the conservative [4 (5.2%) versus 11 (15.3%)], p=0.031), while in the period between discharge and the first 30 days, the percentage of combined events was similar in both groups [1 (1.3%) versus 2 (2.8%), p=NS]. At 12 months, mortality and percentages of combined major events were less in the invasive group [3 (3.9%)

Table 3. Endpoints analysis in the two treatment strategy groups.

	Group A –invasive treatment (N=76)	Group B-conservative treatment (N=72)	P value
In-hospital outcome-no (%)			
Stabilisation	73 (96)	31 (43)	0.0001
Non-fatal MI	2 (2.6	3 (4.2)	NS
Death	1 (1.3)	6 (8.3)	0.046
Combined event	3 (3.9)	9 (12.5)	0.053
Hospitalisation (days)	11.4±6.3	12.4±8.0	NS
Outcome at 30 days-no (%)			
Non-fatal MI	2 (2.6)	3 (4.2)	NS
Death	2 (2.6)	8 (11.1)	0.030
Combined event	4 (5.3)	11 (15.3)	0.031
Outcome at 12 months-no (%)			
Non-fatal MI	3 (3.9)	3 (4.2)	NS
Death	3 (3.9)	9 (12.5)	0.053
Combined event	6 (7.9)	12 (16.7)	NS
Readmission (UA)	13 (17.1)	17 (23.6)	NS
Late CA*	18 (23.6)	17 (23.6)	NS
Late PTCA*	12 (15.8)	8 (11.1)	NS
Late CABG*	6 (7.9)	9 (12.5)	NS

MI: myocardial infarction; UA: unstable angina; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting surgery; *: CA (Coronary angiography), PTCA and CABG performed after discharge; NS: non -statistically significant.

versus 9 (12.5%) p=0.053 and 6 (7.9%) versus 12 (16.7%) p=NS], although not statistically significant. Duration of hospitalization did not differ considerably between the two groups [group A: 11.4±6.3 days versus group B: 12.4±8.0 days respectively (p=NS). Mean time for recovery after coronary artery bypass grafting was 9.0±3.9 days. At 12-month follow-up, groups A and B had similar readmission rates [13 (17.1%) versus 17 (23.6%), p=NS] and need for late coronary angiography [18 (23.6%) versus 17 (23.6%), p=NS], coronary angioplasty [12 (15.8%) versus 8 (11.1%), p=NS] and coronary artery bypass grafting [6 (7.9%) versus 9 (12.5%) p=NS].

Analysis of major cardiac events

In group A during hospitalization, one patient died (a patient that continued pharmaceutical treatment after diagnostic angiography) and two patients suffered from non-fatal myocardial infarctions (one Q wave MI and one non- Q wave MI, both patients underwent coronary angiography). In group B, 6 in-hospital deaths occurred (5 before any intervention, 1 after angioplasty). Three of those 6 deaths were due to fatal myocardial infarctions. Three patients of group B suffered non-fatal infarctions (two Q wave MI, one non-Q wave MI) during hospitalization (all prior to invasive treatment). Total incidence (group A + group B patients) of in-hospital deaths and myocardial infarctions related to emergency angioplasty was 1.6% (1/63) and 3.1% (2/63) respectively. None of the patients developed major cardiac events during air-ambulance transfer, while intraaortic balloon counterpulsation was needed in patients with cardiogenic shock. There was no need for emergency coronary artery bypass grafting in patients that underwent on-site angioplasty. None of the 23 patients (group A:19, group B:4) that underwent coronary artery bypass grafting suffered in-hospital death. However, 2 out of 23 patients (both from group A) died shortly after their discharge from the hospital, on the 28th and 32nd day due to peri-operative stroke and heart failure.

Discussion

Patients with refractory unstable angina should be treated either with angioplasty or coronary artery bypass grafting. However, such management is limited by equipment and technical personnel availability that is in a position to perform coronary interventions and surgical processes. A possible solution to this problem is the transfer of patients with unstable angina to third-degree centers with interventional and surgical facilities. Transfer of such patients is feasible in geographically compact areas where distances are short. Modern ambulances may be adequately equipped, while modern intraaortic pumps are portable and may operate with batteries for hours. With the appropriate personnel, the transfer of patients in critical condition may be also possible[3]. However, in geographically isolated areas, the transfer is questionable and sometimes not feasible. The frequent use of air transportation (in our case, 148 patients would have been transferred during a period of 20 months - 1.7 patients per week) is costly, may be dangerous and requires high level organization. Also, there is no experience regarding safe air-transfer of patients with unstable angina. Under these conditions, the existence of small, independent angioplasty units is justified and decrease the number of patients that need air-ambulance transfer. Such units already exist and treat only acute myocardial infarctions. Their results can be compared to those of large units, indicating that the lack of cardiac surgery alone does not limit the application, safety and effectiveness of angioplasty in these patients[9-12]. No experience is stated regarding treatment of patients with unstable angina in geographically isolated centres without on-site cardio-surgical equipment.

The TRUCS study is the first randomised clinical study that compares invasive (on-site coronary angioplasty or emergency air-ambulance transfer for acute coronary artery bypass grafting) versus conservative treatment (persistence in pharmaceutical treatment) for the management of patients with refractory unstable angina in geographically isolated areas without cardiac surgery back-up. Three previous published randomised studies (TIMI 3B, VANQWISH and FRISC-II) have compared the role of early invasive versus conservative treatment in patients with unstable angina[15-17]. All patients with persisting symptoms were excluded from these studies and were treated invasively. The TRUCS study showed that the combination of on-site angioplasty and emergency air-ambulance transfer for urgent coronary artery bypass grafting provides advantages against the persistence in pharmaceutical treatment in this group of high-risk patients. Individuals that were treated invasively showed lower incidence of death and fatal myocardial infarctions during hospitalization and within

30 days after discharge. Mortality within 12 months in the invasively treated group of this study was similar to the one reported in studies TIMI IIIB and FRISC-II (3.9% versus 4.1% and 2.2% respectively). It should be noted that the sample size in our study was relatively small and that one more major cardiac event in group A or one less major cardiac event in group B would have concluded to a non-statistically significant result. This difference, however, is not likely to be accidental because incidence of death and myocardial infarction in the conservatively treated group was expected to be higher than the one reported. The relatively low incidence of myocardial infarction and death of patients randomized to conservative treatment (which by definition had already failed) was likely due to the high percentage of patients who switched to invasive treatment. During follow-up at 12 months, mortality and combined outcome tended to be lower in patients of group A, although there was no difference in non-fatal myocardial infarctions between the two groups. In this study, the duration of initial hospitalization, readmission of patients due to unstable angina as well as the number of patients that underwent, after their initial discharge from hospital, any revascularization intervention (coronary angioplasty and coronary artery bypass grafting) does not differ in the two groups. Our results support the hypothesis of independent intervention units in geographically isolated areas for the management of patients with refractory unstable angina. Angioplasty, using technology that is available today (low profile flexible intracoronary stents, IIb/IIIa inhibitors, intraaortic pumps) can be performed with safety (percentage of death and myocardial infarction 1.6% and 3.2% respectively) in centers without cardiac surgery back-up (in the same or in a nearby hospital). During air-ambulance transfer of patients for urgent coronary artery bypass grafting, no death or fatal infarction occurred (even in patients that needed intraaortic pump) making the service of urgent air transportation a feasible alternative strategy, when available and weather permitting.

Transfer of patients for urgent angioplasty was not examined in this study. However, with such policy, the additional cost and burden of such a service would have been a restrictive factor and the consequences regarding the safety of the patients would have been unknown.

Conclusion

Interventional management of patients with refractory unstable angina in isolated areas without cardiac surgery back-up significantly increased in-hospital stabilization and reduced major events during hospitalization, at 30 days and at 12 months. The present study proposes that coronary angioplasty in independent units, as well as, emergency air-ambulance transfer of patients with unstable angina are safe.

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