THROMBOLYSIS IN MYOCARDIAL ISCHEMIA

MANUAL OF OPERATIONS

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CHAPTER 12

GUIDELINES FOR STANDARD CLINICAL CARE

12.1 GUIDELINES FOR CONVENTIONAL THERAPY IN T3A

12.1.1 Introduction

Guidelines have been established for the conventional therapy (i.e., all therapy other than t-PA, t-PA placebo, angiography and revascularization) of patients enrolled in T3A. The purpose of these guidelines is to minimize variability in conventional therapy and thereby increase the likelihood that positive or negative effects of t-PA therapy can be detected. The guidelines specify the type of agent to be given (if the clinical situation permits) and the starting dosage. They are in effect from the time of enrollment to the completion of the follow-up angiogram.

12.1.2 General Measures

All patients enrolled in the study will receive standard CCU care, including bedrest and oxygen.

According to the FDA, the use of any investigational (non-FDA approved) drug or device on T3 patients is proscribed until complete ascertainment of the primary end point for each study drug has been obtained. For T3A patients, experimental devices or drugs may not be used until after the second coronary angiogram has been completed (18 to 48 hours after treatment).

12.1.3 Heparin

The goal is to administer intravenous heparin therapy to maintain the APTT 1.5 to 2 times normal. If the patient is already receiving heparin at the time of enrollment, the prior dosage should be continued, the APTT determined and the dosage adjusted according to the guidelines presented below. If at all possible, heparin therapy should be started before study treatment. If heparin therapy has not been started prior to study treatment, it should be started as soon as possible and within

one hour of the start of study treatment, in a bolus of 5,000 IU intravenously followed by an infusion at the rate of 1,000 IU per hour to be adjusted by APTT values (determined 3 hours after a change in heparin dosage and every 12 hours on maintenance therapy) to a level 1.5 to 2 times normal. Changes in dosage should be as follows:

APTT	Adjustment
3x control	Decrease infusion rate by 50%
2-3x control	Decrease by 25%
1.5-2x control	No change
< 1.5x control	Increase rate of infusion by 25% to a maximum rate of 2,500 units/hour

Four hours prior to the first angiogram, for which an arterial puncture must be performed, the heparin dosage should be reduced to 50% of the maintenance level. After the arterial sheath has been placed, a 5,000 IU dose of heparin should be administered intravenously and the full maintenance dose resumed one hour after the bolus. The sheath should be left in place until completion of the follow-up angiogram.

12.1.4 Anti-Ischemic Therapy

At the time of enrollment, therapy with a beta-adrenergic blocking agent, a calcium channel blocker and a nitrate preparation should be initiated, if not already being given. If the patient was receiving and tolerating an agent from these classes of drugs prior to enrollment, the same agent and dosage should be continued. If the patient was not receiving an agent from each of these classes, and the clinical situation permits, the following agents should be given.

Beta-adrenergic blockade - Metoprolol 50 mg po q 12 h.

Calcium Channel blockade - Diltiazem 30 mg po q 6 h. Diltiazem should not be given if evidence of left ventricular dysfunction is present.

Nitrate therapy - Isosorbide dinitrate 10 mg po q 6 h.
Sublingual TNG prn.

(NOTE: Diltiazem has been selected as the calcium antagonist for conventional therapy because it is the only agent in this class reported to reduce the incidence of reinfarction. Metoprolol has been selected based on evidence that it is beneficial for the therapy of acute myocardial infarction.)

If ischemic symptoms occur after enrollment, the dose of the above agents should be increased as clinically indicated. Intravenous nitroglycerin is not to be used as routine initial therapy for unstable angina or non-Q-wave infarction. It may be continued if required prior to enrollment, and initiated if clinical indications develop after enrollment. Intra-aortic balloon counterpulsation should not be utilized unless patients develop symptoms refractory to the above-mentioned therapy.

12.1.5 Aspirin

Aspirin will not be given routinely during the T3A protocol since all patients will be receiving heparin, and aspirin may increase the risk of hemorrhage during t-PA therapy. If PTCA is likely to be performed immediately after the follow-up angiogram is obtained, aspirin (325 mg) may be given orally four hours prior to the PTCA. After completion of the follow-up angiogram, aspirin may be initiated if clinically indicated.

12.1.6 Revascularization

Since the purpose of T3A is to evaluate changes in coronary angiographic findings following t-PA therapy, it is important that revascularization (with PTCA or CABG) not be performed electively prior to the follow-up angiogram. If the patient becomes unstable (as determined by the treating physician), emergency revascularization may of course be performed when indicated. It PTCA is chosen for emergency revascularization, the angiogram performed immediately prior to the PTCA

should be conducted in such a manner that it will serve as the follow-up angiogram.

12.1.7 Beta-adrenergic Blockade Guidelines

Contraindications to long-term beta-blocker therapy include the following.

1. Heart rate at rest consistently < 45 beats per minute.
2. Systolic BP consistently < 90 mmHg.
3. Moist rales that do not clear with coughing, involving 1/3 or more of the lung fields interpreted as signs of congestive heart failure, or pulmonary edema with consistent chest X-ray findings.
4. Presence of significant first-degree AV block (P-R > 0.24 sec) or second- or third-degree block (except if permanent pacemaker is in place).
5. Asthma by history of wheezing or by physical examination, or chronic obstructive pulmonary disease requiring chronic therapy with corticosteroids or $beta_2$-stimulants.

Therapy with beta blockers should be stopped if any of the following occur.

1. Lengthening of the PR interval beyond 0.26 seconds or second- or third-degree AV block.
2. Wheezing, rales extending > 1/3 of the way up the lung fields, or pulmonary congestion on chest X-ray.

Therapy with beta blockers will be temporarily withheld (and can be restarted later at lower dose) if any of the following occur.

1. Ventricular rate below 45 beats per minute.
2. Systolic arterial pressure < 90 mmHg.

12.1.8 Guidelines for Treatment of Dysrhythmias

In case of sinus bradycardia < 50 beats per minute (other than that due to beta blocker therapy) with hypotension (BP < 80/60) or other complications, or heart rate < 40 beats per minute without compli-

cations, 0.5 mg atropine IV can be used and repeated, if needed, not to exceed a total dose of 2 mg.

If the ventricular rate is rapid (> 100/min) and is not due to sinus tachycardia, and the patient has either compromised circulation or myocardial ischemia, then cardioversion may be the treatment of choice in case of ventricular or supraventricular dysrhythmia (atrial fibrillation, atrial flutter, ventricular tachycardia, paroxysmal atrial tachycardia). Depending on clinical circumstances, other therapies to be considered for supraventricular dysrhythmia include IV verapamil, metoprolol, propranolol, or digoxin. If patients are already on beta blocker therapy, IV verapamil is not advised.

For ventricular premature contractions (VPC's), unresponsive to lidocaine, a possibility for therapy is procainamide 100 mg every 2-5 minutes IV up to 1 gm while closely monitoring blood pressure, followed by IV drip at 1 to 4 mg per min.

12.1.9 Pacemakers

Indication for pacemakers insertions are:

1. Complete heart block,
2. Mobitz type-II block,
3. Sinus bradycardia (< 40 beats per min) with hypotension not due to beta blocker therapy and not responsive to atropine, and
4. Acute right bundle branch block with left anterior hemiblock or left posterior hemiblock.

12.1.10 Hemodynamic Monitoring

Acute hemodynamic monitoring may be used if clinically indicated for compromised circulation (heart failure or hypotension) or for undiagnosed persistent tachycardia.

12.1.11 Heart Failure

Heart failure (defined as at least pulmonary artery wedge pressure [PAWP] > 18 mmhg, and/or cardiac index [CI] < 2.0) without severe symptoms can be treated with furosemide. If the heart failure is persistent or more severe (persistent dyspnea and rales) or the cardiac index is low ($\leq$ 2.0) and systolic arterial pressure > 90 mmHg, then vasodilator therapy may be used with or without digitalis as clinically indicated.

12.1.12 Cardiogenic Shock

Pressor agents, intra-aortic balloon counterpulsation (IABP), PTCA, and coronary artery bypass graft (CABG) surgery may be used as clinically indicated in case of cardiogenic shock (CI < 2 1/min/m^2, PAWP > 18 mmHg, mean arterial pressure [MAP] < 60 mmHg).

12.1.13 Acute Mitral Regurgitation or Ventricular Septal Defect

Vasodilator therapy, intra-aortic balloon counterpulsation, and corrective surgery may be used as clinically indicated in case of acute mitral regurgitation or ventricular septal defect (VSD).

12.2 GUIDELINES FOR CONVENTIONAL THERAPY IN T3B

12.2.1 Introduction

Guidelines have been established for the conventional therapy (i.e., all therapy other than t-PA, t-PA placebo, invasive strategy or conservative strategy) of patients enrolled in T3B. The purpose of these guidelines is to minimize variability in conventional therapy and thereby increase the likelihood that positive or negative effects of t-PA therapy and the conservative or invasive management strategy can be detected. The guidelines specify the type of agent to be given (if the clinical situation permits) and the starting dosage. They are in effect from the time of enrollment until the six-week follow-up.

12.2.2 General Measures

All patients enrolled in the study will receive standard CCU care, including bedrest and oxygen.

According to the FDA, the use of any investigational (non-FDA approved) drug or device on T3 patients is proscribed until complete ascertainment of the primary end point for each study has been obtained. For T3B patients, experimental devices or drugs may not be used until after the six-week follow-up contact ECG and ETT have been obtained.

12.2.3 Heparin

The goal is to administer intravenous heparin therapy to maintain the APTT 1.5 to 2 times the normal APTT recorded when the patient was not receiving heparin. If the patient is already receiving heparin at the time of enrollment, the prior dosage should be continued, the APTT determined and the dosage adjusted according to the guidelines presented below. If at all possible, heparin therapy should be started before study treatment. If heparin therapy has not been started prior to study treatment, it should be started as soon as possible and within one hour of the start of study treatment, in a bolus of 5,000 IU intravenously followed by an infusion at the rate of 1,000 IU per hour to be adjusted by APTT values (determined eight hours after the initial heparin bolus; determined three hours after a change in heparin dosage; and every 12 hours on maintenance therapy) to a level 1.5 to 2 times normal. Changes in heparin dosage should be managed as follows:

APTT	Adjustment
> 3x control	Decrease infusion rate by 50%
2-3x control	Decrease by 25%
1.5-2x control	No change
< 1.5x control	Increase rate of infusion by 25% to a maximum rate of 2,500 units/hour

Four hours prior to the angiogram for which an arterial puncture must be performed, the heparin dosage should be reduced to 50% of the

maintenance level. After the arterial sheath has been placed, a 5,000 IU dose of heparin should be administered intravenously and the full maintenance dose resumed one hour after the bolus. Heparin will be discontinued 72 hours after treatment unless other clinical indications warrant earlier termination or continued administration. For example, if the patient is found to have normal coronaries, medical treatment including anti-anginal medications and heparin is physician directed. Measurements of platelets, hemoglobin and hematocrit should be obtained every 24 hours while patient is on maintenance heparin therapy.

Following angiography, heparin therapy should be continued and the sheath left in place for 48 hours if possible. Heparin therapy should be stopped four hours prior to removal of the arterial sheath. If the sheath must be removed sooner than 48 hours after angiography, the heparin dose should be reduced to 50% of maintenance four hours prior to sheath removal, and the artery held for at least 30 minutes.

After the start of the heparin infusion, the conventional anti-ischemic medications described below will be initiated (if not given prior to enrollment).

12.2.4 Anti-ischemic Therapy

At the time of enrollment, therapy with a beta-adrenergic blocking agent, a calcium channel blocker and a nitrate preparation should be initiated, if not already being given. If the patient was receiving and tolerating an agent from these classes of drugs prior to enrollment, the same agent and dosage should be continued. If the patient was not receiving an agent from each of these classes, and the clinical situation permits, the following agents should be given.

Beta-adrenergic blockade -	Metoprolol 50 mg po q 12 h.
Calcium Channel blockade -	Diltiazem 30 mg po q 6 h. Diltiazem should not be given if evidence of left ventricular dysfunction is present.

Nitrate therapy - Isosorbide dinitrate 10 mg po q 6 h.
Sublingual TNG prn.

(NOTE: Diltiazem has been selected as the calcium antagonist for conventional therapy because it is the only agent in this class reported to reduce the incidence of reinfarction. Metoprolol has been selected based on evidence that it is beneficial for the therapy of acute myocardial infarction.)

If ischemic symptoms occur after enrollment, the dose of the above agents should be increased as clinically indicated. Intravenous nitroglycerin is not to be used as routine initial therapy for unstable angina or non-Q-wave infarction. It may be continued if required prior to enrollment, and initiated if clinical indications develop after enrollment. Intra-aortic balloon counterpulsation should not be utilized unless patients develop symptoms refractory to the above-mentioned therapy.

Conventional anti-ischemic therapy should be continued, if clinically indicated, despite randomization to early, routine angiography and possible revascularization. It should be continued by protocol until the six-week follow-up.

12.2.5 Aspirin Therapy

Aspirin will not be administered routinely during the first 24 hours after enrollment and possible t-PA therapy. (All patients will receive heparin during this period.) On day 2, aspirin will be administered orally in a dose of 325 mg daily and continued by protocol until the six-week follow-up. The Ecotrin preparation of aspirin will be utilized for the 325 mg dosage. If the patient is unable to take aspirin, the treating physician should direct oral anticoagulant therapy.

12.2.6 Angiography and Revascularization

Since a purpose of T3B is to compare a conservative versus invasive approach to management of these patients, it is important that

angiography be performed only if indicated by the protocol. With the invasive approach, all patients will receive early angiography. With the conservative approach, angiography should be performed if, and only if, initial therapy fails to control spontaneous or provokable ischemia as defined by the protocol. Revascularization with PTCA or CABG will be guided by the angiographic findings (see Chapter 4, Section 4.4.3.1 - Routine Early Angiography and PTCA/CABG). Angiography, PTCA or CABG performed for other indications is a protocol violation and will be monitored. Routine anti-anginal therapy after revascularization is physician directed.

12.2.7 Beta-adrenergic Blockade Guidelines

Contraindications to long-term beta-blocker therapy include the following.

1. Heart rate at rest consistently < 45 beats per minute.
2. Systolic BP consistently < 90 mmHg.
3. Moist rales that do not clear with coughing, involving 1/3 or more of the lung fields interpreted as signs of congestive heart failure, or pulmonary edema with consistent chest X-ray findings.
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Therapy with beta blockers should be stopped if any of the following occur:

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12.2.11 Heart Failure

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12.2.12 Cardiogenic Shock

Pressor agents, intra-aortic balloon counterpulsation (IABP), PTCA, and coronary artery bypass graft (CABG) surgery may be used as clinically indicated in case of cardiogenic shock (CI < 2 1/min/m^2, PAWP > 18 mmHg, mean arterial pressure [MAP] < 60 mmHg).

12.2.13 Acute Mitral Regurgitation or Ventricular Septal Defect

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