

A Novel Treatment for Intractable Angina: High Thoracic Epidural Analgesia

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Citation

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Abstract

INTRACTABLE ANGINA: SCOPE OF THE PROBLEM AND CURRENT TREATMENT

Despite improvements in the medical and surgical treatment of coronary artery disease, there continues to be a subset of patients who are refractory to standard, established treatment modalities. These patients are markedly debilitated, require frequent hospitalizations, and consume significant amounts of economic resources. A variety of surgical and medical treatments have been employed in an attempt to improve the quality of life of these patients. Left sided stellate ganglion blocks, surgical sympathectomy, transmyocardial laser revascularization, enhanced external counter pulsation, transcutaneous electrical nerve stimulator therapy (TENS) and chelation therapies have all been utilized (1,2). Each of these procedures has significant limitations and/or associated complications.

A recently developed surgical approach to the treatment of these patients is transmyocardial laser revascularization. This treatment requires the performance of a sternotomy under general anesthesia is difficult to use in seriously ill patients especially those with a low ejection fraction (2). Cooley et al described long term patency of laser-formed coronary artery channels in a post mortem case report (3), however the results of randomized trials are not yet available. Surgical sympathectomy, not frequently performed in this decade, also requires general anesthesia and may be complicated by a permanent Horner's syndrome, pneumothorax, thoracic duct injury, dural tears and infection (4). Stellate ganglion blocks are effective in reducing anginal frequency but provide only temporary relief even when lytic solutions are used. TENS therapy has been shown to be effective in diminishing pain. TENS treatment is safe; however, it is inconvenient and patients often become sensitive to the electrode gel. The exact mechanism of action

of TENS is unclear and inadequately studied.

HIGH THORACIC EPIDURAL ANALGESIA: NEW TREATMENT FOR INTRACTABLE ANGINA

In the mid-1980's, Blomberg and colleagues investigated the efficacy of high thoracic epidural analgesia (HTEA) for patients with severe angina (1,5). Twenty patients were treated with HTEA and followed for six months to 3.2 years. An implantable Port -a-Cath device coupled to a tunneled epidural catheter was placed at a T1-5 position. The system was designed so that the analgesic agent would be administered by intermittent bolus injection by the patient using a standard needle and syringe. These patients received HTEA either while awaiting coronary artery bypass (CABG) surgery, or angioplasty, or because they were inoperable and refractory to all medication regimes. The patients' administered 3-5 milliliters of 0.5% bupivacaine to themselves no more frequently than every two hours and did not exceed three doses per day. All patients reported improvement in the quality of life and no significant side effects or complications. Of the 20 patients studied, five died during the follow-up period; however, none of the deaths were related to the HTEA treatment (1).

Continuous infusion HTEA therapy has also been shown to be effective in helping to control the ischemic pain associated with acute myocardial infarction when it is refractory to standard treatments administered in the intensive care unit (6). Additionally, Liem et al described the beneficial effects of HTEA during CABG surgery which include a decrease in intra and postoperative ischemia, maintaining hemodynamic stability and providing postoperative relief of surgically related pain (7,8,9,10).

HTEA: MECHANISMS OF ACTION

The effects of HTEA on coronary artery hemodynamics has

been studied both in patients with CAD and animal models of ischemic heart disease. Using canine models of ischemic heart disease, Klaussen et al (¹¹) and Davis et al (¹²) showed that HTEA treatment improved myocardial blood flow and transmural flow distribution during partial coronary ligation and reduced myocardial infarction size during total coronary ligation.

Clinical studies showed that HTEA may increase myocardial blood flow (supply) while decreasing myocardial oxygen consumption (demand). For example, Blomberg et al demonstrated that the luminal diameter of stenotic coronary vessel segments increased from 1.34 to 1.55 mm with HTEA. However, HTEA had no effect on the luminal diameter of normal coronary vessel segments (¹³). This fact is important because it suggests that HTEA, by not increasing myocardial blood flow in normal coronary arteries, will not result in shunting blood away from diseased vessels causing “coronary steal” and will not increase CAD related ischemia. Furthermore, Heush et al (^{14,15}) showed that HTEA may increase myocardial blood flow by decreasing the progressive reflex sympathetic vasoconstriction which often exists distal to a coronary stenosis and can act to aggravate the myocardial ischemia caused by this stenosis.

In addition to altering myocardial blood flow, Blomberg et al showed that HTEA caused a decrease in the determinants of myocardial oxygen demand by causing a decrease of systolic arterial pressure, heart rate, and pulmonary capillary wedge. These changes in hemodynamics did not adversely effect coronary perfusion pressure or cardiac output both of which were not significantly changed by HTEA. These data suggest that the beneficial effects of HTEA may result from alterations in the myocardial oxygen supply / demand ratio both by increasing transmural myocardial coronary blood flow and by decreasing oxygen demand (^{13,16}). These changes in the relation between myocardial oxygen supply and demand may not only decrease ischemia, but may also improve and preserve global and regional left ventricular function (¹⁷). Kock et al showed that treatment with HTEA improved global and regional LV function during stress induced myocardial ischemia in patients with coronary artery disease (¹⁷).

INITIAL PATIENT TREATED AT MUSC

In 1994, we treated our first patient with HTEA. He was a 44 year old man who had been hospitalized in the ICU at the Ralph H. Johnson Department of Veterans Affairs Medical Center for two weeks. He was not a candidate for surgical or

catheter based revascularization. He was refractory to maximal medical treatment. Any attempt to discontinue the intra-aortic balloon pump or the intravenous nitrates or heparin resulted in severe angina and myocardial ischemia with inferior T- wave changes. Therefore, the decision was made to treat this patient with HTEA. A flex tip-plus catheter (Arrow) was placed at a T3 level (position confirmed by CT scan) after IV heparin had been discontinued and the coagulation profile had normalized. Immediately after catheter placement, the patient received a bolus dose of bupivacaine followed by a continuous infusion for several hours thereafter. Then the patient was injected with four cc of 0.25% bupivacaine through the catheter whenever the patient complained of chest pain. The patient was taught to inject the catheter himself using pre-filled syringes at given intervals of at least 180 minutes with doses not exceeding four times per day. During the following 24 hrs IV nitrates and heparin were discontinued. Gradually the patient was allowed to ambulate freely. Surveillance ECG's and cardiac enzymes were performed during the remainder of the hospitalization and there was no new evidence of myocardial ischemia or injury. During the next 2 weeks, the patient's activity level increased and he had infrequent recurrences of angina. After two weeks, we replaced the flex tip plus catheter with a catheter designed for long term use - a DuPen catheter (Bard). The patient was trained in the use of this new catheter and was monitored using home health nurses along with office visits with a physician. This success resulted in the anesthesia department receiving more than 30 consults for treatment of intractable angina with HTEA in the ensuing three years.

DEVELOPMENT OF INTRACTABLE ANGINA CLINIC

We established an Intractable Angina Clinic at the Medical University of South Carolina and Ralph H. Johnson Department of Veterans Affairs Medical Center to provide comprehensive patient care to these problematic patients. The clinic is associated with the Anesthesiology Pain Clinic and is thus equipped to handle invasive procedures and detailed clinical patient follow up. Patient evaluation and the development of treatment plans for each patient are provided in collaboration with members of anesthesia, cardiology, cardiovascular surgery, psychiatry and neurosurgery. Clinical protocols were designed to document the presence of reproducible ischemia (dobutamine stress thallium), document anginal exercise threshold (Naughton ETT), and the frequency of silent ischemia (24 hour Holter ST segment analysis). These assessments were performed before and

after the start of HTEA treatment. Prior to the start of HTEA treatment, reevaluation for surgical or coronary artery revascularization and adequacy of the medical regimen are provided.

Placement of the more permanent catheter delivery devices (the DuPen and Epiport [Deltec] catheters) is performed in the operating room with the assistance of a neurosurgeon. The medication is delivered using a PCA CADD pump (Deltec). This device has an important safety measure which mandates a prescribed minimum time between doses and prevents too frequent treatment. The pharmacies and home health nursing organizations which we use have been provided with very specific outlines and treatment protocols.

After the above evaluation, specific selection criteria are used to determine appropriate use of HTEA. We do not treat all patients with HTEA. The patient must understand and properly use the PCA pump, learn the limitations of HTEA therapy, and be willing to be compliant with follow-up care. The patient must learn the risks of HTEA treatment and must be willing and able to detect any symptoms of epidural infection or hemorrhage. Co-morbidities such as diabetes, chronic steroid use and long term anticoagulation may increase patient risk during HTEA and sometimes require the use of alternate treatment modes such as TENS unit or the use of chronic long-term narcotics.

The type of catheter chosen for a given patient is dependent upon the acuteness of the patient's condition and the expected length of time the catheter may be needed. For example, a Dupen catheter will be used when it is expected that the duration of treatment will be weeks to months or if it is unclear if the patient will remain compliant. If the duration of treatment is expected to exceed a year, then a fully implantable Epiport system will be used. With few exceptions, all patients receive a trial of therapy with a temporary flextip plus catheter (Arrow) for one to two weeks. Before placement of a more permanent catheter, this one-two week trial period allows us to evaluate the effectiveness of HTEA in treating and preventing recurring anginal symptoms, provides the opportunity for patient education, gives the patient a period of time to make necessary lifestyle changes and reach a conclusion to support this approach to treatment. Physician and nursing follow-up occurs two times/week for 4 weeks, then decreases to one/month by 4-6 weeks.

REVIEW OF INITIAL UNSTABLE ANGINA

PATIENT SERIES AT MUSC/VAMC

We recently reviewed the results of HTEA treatment in our first 10 patients. These eight men and two women, mean age 58 years, all had extensive three vessel coronary artery disease and New York Heart Association (NYHA) class IV symptoms of angina. These patients were refractory to medical management and were not candidates for surgical or catheter based revascularization. Medical therapy included oral nitrates, beta-blockade, calcium channel blockers and narcotics. Prior to HTEA, two patients required an intra-aortic balloon pump, seven patients required continuous IV heparin and nitroglycerin for angina control. HTEA was performed at the T1- T4 levels with radiologic confirmation. Bupivacaine (0.25%-0.5%) was used in an initial bolus of 3-5 cc followed by either a continuous infusion or intermittent bolus therapy. Four patients were treated for seven days, three patients for fourteen days, and three patients greater than 90 days. All ten patients had improvement in their symptoms after initiation of HTEA. Five patients improved to NYHA class II and five improved to NYHA class III symptoms of angina. All seven patients who were on IV heparin and nitroglycerin and the two patients being treated with an intra-aortic balloon pump were able to have these modalities discontinued, underwent gradual ambulation and hospital discharge. There was one death in this group. This death was not catheter related. There were three catheter complications which were due to local infection, fibrosis at the catheter tip and back spasms. The catheters were successfully removed in these three patients and the complications resolved. Of significant interest, none of the ten patients had a myocardial infarction or significant arrhythmia during the period of catheter therapy (18). As of July 1997, we have placed 25 catheters in patients to treat refractory angina and have had similar results.

ADDITIONAL INDICATIONS FOR HTEA TREATMENT

In addition to using HTEA to treat patients with intractable and refractory angina who are not candidates for standard revascularization, we have used HTEA to treat patients with refractory angina who are candidate for definitive surgical procedures but whose definitive treatment must be delayed for a period of time. In these patients, HTEA was used as a "temporizing" measure used to stabilize patients until definitive treatment can be instituted. Two examples of this indication include 1) patients with refractory angina who are awaiting heart transplant or 2) patients with refractory

angina but whose co-morbidities prevent revascularization from being instituted at a reasonable risk and in who delay of such procedures would allow time for resolution of these co-morbidities and effectively reduce the risk for these definitive therapies. We describe three such patients below. The first patient had extensive coronary artery disease which was not amenable to revascularization, an ischemic cardiomyopathy, and intractable refractory and debilitating angina. The severity of his symptoms required frequent and recurrent hospitalizations and office visits. Essentially the patient was bedridden despite high dose narcotic therapy. To provide temporizing palliative treatment, HTEA was instituted using a Dupen catheter. HTEA provided adequate palliation, reduced the level of narcotic use, prevented recurrent hospital admission and allowed a moderate level of physical activity. The HTEA treatment was continued for 108 days. Because this patient was pre-heart transplant, a number of additional procedures were instituted to prevent infection and other complications which would raise the risk of increased morbidity or mortality associated with transplantation and post-transplantation immunosuppression. For example, 0.22 micron filters placed between the catheter port and tubing were changed every three days, and bupivacaine solutions and tubing to the catheter were changed every five days. Prophylactic antibiotics (ciprofloxacin 500 mg. b.i.d. or cephalexin monohydrate 250 mg. q.i.d.) were administered if any breach in sterility was noted, i.e., disconnection of tubing or unsterile access procedures. HTEA was continued postoperatively for two days to provide surgical pain control. The catheter was then removed. There were no complications throughout the course of the treatment, in particular, there was no evidence of epidural infection, abscess formation, or epidural fibrosis.

The second patient was also awaiting a heart transplant. He had an ischemic cardiomyopathy and remained in the intensive care unit at an outside institution because of refractory angina for 8 weeks on IV nitroglycerin, heparin and high dose narcotics, prior to HTEA treatment. He was transferred to our institution for transplant evaluation. HTEA treatment was begun using a Flexitip Plus catheter. The IV nitroglycerin, heparin and narcotics were discontinued, the patient was progressively ambulated, evaluated for transplant and the antianginal and CHF medical regimens were optimized. He was awaiting placement on the transplant list. HTEA was continued using an Epiport. The patient was discharged to home. After 6 months of treatment with HTEA and the institution of cardiac rehabilitation, the patient's anginal symptoms markedly improved. His HTEA

therapy was discontinued and he was no longer considered a transplant candidate.

The third patient had extensive three vessel CAD, severe intractable angina but coronary anatomy amenable to surgical revascularization. Treatment included nitroglycerin, heparin, narcotics, and an intra-aortic balloon pump. Despite these treatment measures the patient remained severely symptomatic. While coronary bypass grafting was feasible from a technical point of view, the patient had concomitant acute renal failure, pneumonia and congestive heart failure, all of which raised the operative risk to an excessive extent. At the time it was felt that these co-morbidities were treatable and the risk of coronary artery bypass grafting would be substantially reduced if surgery could be postponed. The ischemic burden could not be reduced by PTCA for technical reasons. For this reason, HTEA treatment was begun using a Flexitip catheter placed at T3 and a continuous bupivacaine infusion of 0.068% (we now use much higher concentrations) together with .1 mg/ml morphine at 4 cc/hr. The addition of morphine helped cover physical pain due to procedures. HTEA markedly reduced the symptoms of angina, and within 48 hours the IV nitroglycerin, heparin, narcotics were discontinued and intra-aortic balloon pump was removed. After 4 days, the continuous infusion was replaced with intermittent bolus therapy. Over the 20 day treatment with HTEA, the acute renal failure and pneumonia resolved, the congestive heart failure was adequately controlled, and the patient underwent successful coronary artery bypass grafting surgery (19). Surveillance ECG's and cardiac enzymes confirmed the fact that no myocardial injury occurred during HTEA treatment. Subsequently, we have successfully treated 5 patients with similar indications.

SUMMARY

To date, 25 patients with intractable, refractory angina have been successfully treated with HTEA at our institution. Indications included both patients unable to undergo revascularization because of unsuitable coronary anatomy and because of excessively high surgical risk. In the former patients HTEA was used as definitive treatment to control angina. In the later patients HTEA was used as a temporizing measure until the surgical risk for definitive surgical revascularization was acceptable. In addition, HTEA was used as a temporizing measure prior to heart transplantation. There have been no HTEA related deaths, no myocardial infarctions, and no neurological complications. Anginal symptoms have been well controlled in 25 patients

and exercise tolerance has markedly increased. The number of hospitalizations and outpatient visits have been significantly reduced. Thus, we feel that HTEA is a safe and effective treatment for patients with intractable, refractory angina. The exact mechanisms by which anginal control is accomplished by HTEA has not been extensively studied and will require further investigation. However, because our studies and those of other investigators suggest that HTEA holds significant promise, larger scale randomized trials should be undertaken to evaluate the effectiveness of HTEA treatment.

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