Original Article

Safe, Compact and Portable System for Regional Chemotherapeutic Hyperthermic Perfusion Procedures

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ABSTRACT

Perfusion techniques utilizing hyperthermic chemotherapy have been established as a successful modality of therapy for isolated metastatic malignant melanoma. The combination of chemotherapeutic agents (Dactinomycin, thiotepa and Mechlorethamine HCl) given in high doses, not possible systemically, combined with hyperthermia (40-42°C) in an isolated extremity has shown greater tumor regression compared with systemic medication only.

Many of the isolated limb perfusion procedures are performed in non-cardiac centers, especially at specialized cancer institutions. This often presents new obstacles for the perfusionist including lack of adequate perfusion equipment and disposables. Other obstacles include unfamiliarity of the operating room staff with the heart-lung machine and inappropriate and/or unsafe handling of the perfusion circuit. In order to overcome these obstacles and enhance safety, portability and effectiveness, the authors have developed an isolated limb perfusion system.

The purpose of this study was to compare the parameters of treatment and long term outcomes demonstrated by our system and method, to previously published data. The qualitative comparative analysis was performed between eight treatments with this type of perfusion system and outcome data previously published. It is the authors' conclusion that the portable isolated limb perfusion system achieved all of the required parameters to provide safe and effective treatment for this type of melanoma. No demonstrated variation of the long term clinical results in our patient population was seen when compared to previously published data.

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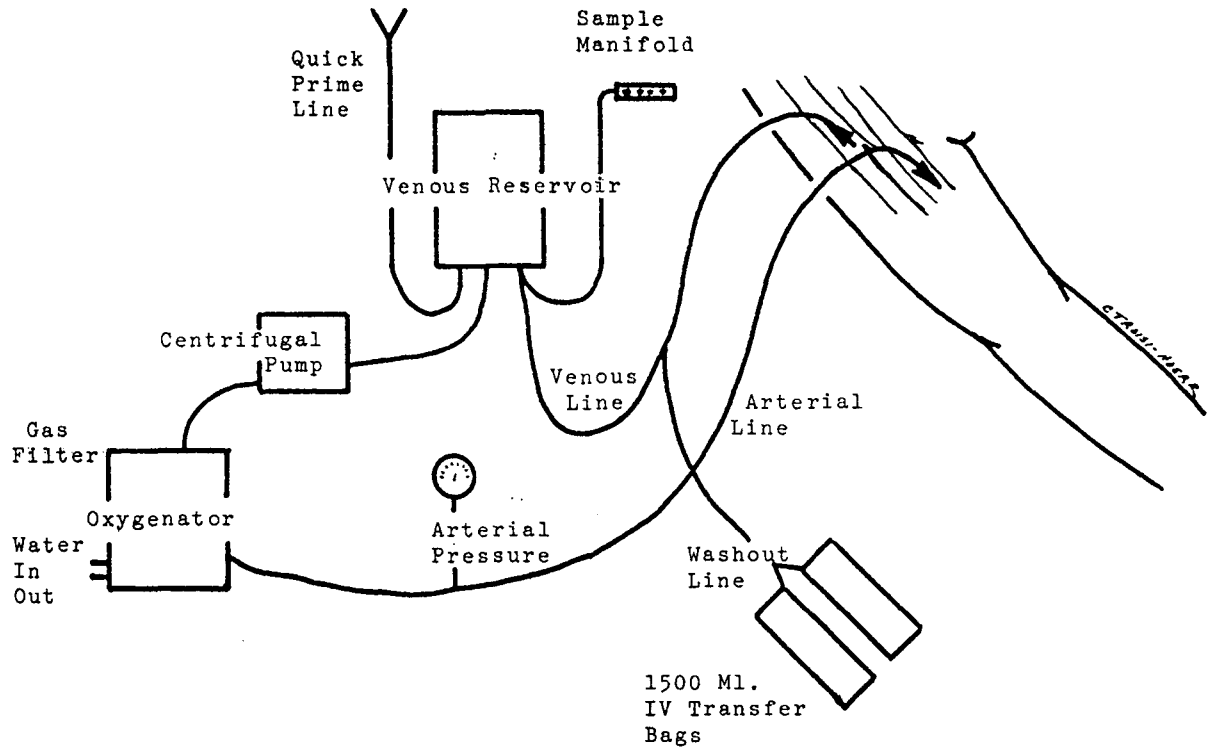
Figure 1
Perfusion Circuit



INTRODUCTION

Regional hyperthermic chemotherapeutic perfusion in treatment of metastatic melanoma of the extremity is a well established modality of therapy. In the tertiary care center which offers both oncologic and cardiac surgery, the perfusion team is generally responsible for the set-up and operation of the isolated limb perfusion system. However, in the cancer center, cardiopulmonary bypass is almost never utilized. In this setting, it is usually difficult to offer isolated limb perfusion treatment due to the lack of proper equipment, disposables and personnel. The capability to offer a portable and safe perfusion system for isolated limb perfusion in the non-cardiac center may make this choice of treatment more readily available to a larger number of patients who present with metastatic melanoma of the upper or lower extremity.

Regional perfusion was first attempted over thirty years ago, as reported by Stehlin and Clark (1). Initial success was limited, and recurrence of the tumor was high. The literature describes two types of tumor recurrences. The first is satellitosis or localized tumor within three centimeters of the scar of the previous melanoma. The second is an in-transit metastasis, occurring between the prior occurrence and the regional lymph node (2). It is reported that the prognosis of recurrent malignant melanoma is poor. The reported survival rates over a five year period, for recurrent tumor have been as low as fourteen percent (3). The combination of toxic doses of chemotherapeutic agents and hyperthermia isolated to the affected limb has shown a much greater rate of complete kill of the tumor cells than conventional treatment or chemotherapy alone. Current regional perfusion generally consists of a high dose chemotherapeutic drug regimen combined with heating of the blood circulating in the isolated perfusion circuit and extremity to 40-42°C. The isolated perfusion time averages 60-100 minutes.

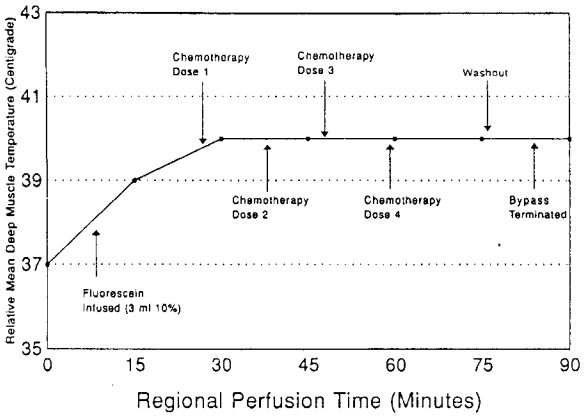
In this study, a simple perfusion circuit was constructed on a mobile cart to allow uncomplicated isolated limb perfusion at the non-cardiac center. The perfusion circuit consisted of a centrifugal pump and a membrane oxygenator/ high efficiency heat exchanger, interfaced with a high-flow water heating unit.

MATERIALS AND METHODS

Seven patients* (8 perfusion treatments) received isolated perfusion therapy. Each of the patients was diagnosed with metastatic melanoma of either the upper or lower extremity. The

* One patient received regional perfusion therapy twice within a 10 month period for a tumor reccurrence.

Figure 2
Perfusion Parameters



patients were given the option of treatment with conventional means or regional perfusion followed by excision of the melanoma. The patients unanimously consented to the perfusion therapy. The patients were transported to the operating room, where arterial and venous monitoring lines were inserted, intravenous lines placed and general endotracheal anesthesia consisting of a combination of fentanyl citrate, pancuronium bromide and inhalation agents was administered. The patients were then surgically prepped with a betadine scrub of the affected limb, the chest, neck and upper abdomen for upper extremity lesions, and the groin, gluteal area and abdomen for lower extremity lesions. Surgical incisions were made to expose the axillary artery and vein for upper extremity perfusion, or the external iliac vessels for lower extremity perfusion. A heparin dose of 300 units/kg body weight was administered, and an ACT of over 480 seconds was established. Additional heparin was administered, as indicated. The respective artery was cannulated with a 12-16 french arterial cannula[a] and the respective vein with a 16-20 french venous cannula[a]. Connection of the previously primed regional perfusion circuit and the cannulated artery and vein was carefully carried out to assure an air-free interface between the cannula and perfusion circuit.

The portable perfusion circuit consisted of both equipment and disposables (Figure 1). The integrated equipment included a modified hospital cart, a Biomedicus 520 centrifugal pump[b] a Sechrist air-oxygen blender and a Normotherm heater unit[d]. The disposable circuit included the Bard HF-5000 membrane oxygenator[a], Biomedicus BP-50 pediatric centrifugal head[b], Terumo CXVRA04 400 ml venous reservoir[e] and a Bard custom tubing set[a]. ACTs were measured with a Hemochron ACT machine[f]. PO_2 and PCO_2 were controlled with the Sechrist blender[c]. Temperatures of the extremity, as well as the arterial and venous blood were monitored with a 5 channel temperature monitor[g]. Sterile 15 mm temperature probes were inserted into the deep muscle of the limb being perfused for continuous limb temperature measure[g].

The perfusion circuit was primed with 700 ml Plasmalyte A solution[h], 100 ml 25% albumin and 5,000 units heparin. After the perfusion circuit was primed, the circulating prime was heated to 41°C. Regional perfusion was initiated and blood gases and electrolyte tests were performed. The perfusion was controlled to maintain arterial blood gas values of pH in the 7.3-7.5 range, pO_2 in the 200-400 mmHg range and pCO_2 in the 30-45 mmHg range. Electrolytes were maintained near physiologic norms. Blood flows in the range of 250-950 ml/minute were obtained.

The surgeon then placed the Esmark tourniquet and secured it with Steinman pins. This was performed to isolate the circulation in the affected limb. A single bolus of 3 ml of 10% fluorescein was injected into the perfusion circuit after the Esmark tourniquet was secured. The purpose of this was to verify complete isolation between the limb and systemic circulation. A sterile black light was passed across the limb/systemic circulatory junction to determine if there was any leakage between the two independent circulations. Once isolation was verified, temperature probes were inserted into the deep muscle beds of the isolated extremity. Two temperature probes were placed in the upper medial and lateral areas as well as the lower medial and lateral areas of the limb undergoing treatment.

A sterile warming blanket was then wrapped around the perfused extremity to minimize heat loss. Perfusion continued until extremity temperature was elevated to a minimum of 39°C. Complete warming took approximately 25 minutes. The arterial blood was heated and maintained at 41°C. The circulating water was maintained at 42°C. Chemotherapy was then initiated.

Three chemotherapeutic agents were administered in bolus form. The first drug was 2 mg mechlorethamine HCl. Mechlorethamine HCl, or Mustargen[i] is an antineoplastic nitrogen mustard displaying cytotoxic action which inhibits rapidly proliferating cells. The second preparation administered was 8 mg Thiotepa[j]. Thiotepa is a cytotoxic agent, pharmacologically related to nitrogen mustard. Its radiomimetic action is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. The third drug administered in succession was 0.2 mg dactinomycin[h]. Dactinomycin, or

a Bard Cardiopulmonary, Tewksbury, MA 01876
b Medtronic Cardiopulmonary, Anaheim, CA 92807
c Sechrist, Anaheim, CA 92807
d Cincinnati Sub-Zero Products Inc., Cincinnati, OH 45241
e Terumo Medical Corp., Piscataway, NJ 08873
f International Technidyne Corp., Edison, NJ 08820
g Sorin Biomedical Inc., Irvine, CA 92714
h Baxter Healthcare Corp., Deerfield, IL 60015
i Merck Sharp and Dohme, West Point, PA 19486
j Lederle Laboratories, Wayne, NJ 07470

Table 1
Patient Demographics

Number of Procedures	8.0*
Male	4.0
Female	3.0
Mean Age	51.7 years
Mean BSA	1.84m^2
Extremity Involved	
Upper	1.0
Lower	7.0
Pre-Op Tumor Classification	
Class III	4.0
Clas IV	4.0

* One patient received regional perfusion twice over a 10 month period for tumor recurrence.

Table 2
Treatment Response

	>6 Months	>1 Year
Complete Regression	5	6
Partial Regression	1*	0
Progression	1	1

* Patient presented with satellitosis at 10 months and was reperfused which resulted in complete regression of the melanoma.

Table 3
Perfusion Parameters

Mean Perfusion Time	81.5 min
Mean Warming Time	29.2 min
Mean Blood Flow	
Upper Extremity	275.0 ml/min
Lower Extremity	910.0 ml/min
Temperature	
Mean Blood	41.1°C
Mean Medial	39.9°C
Mean Lateral	39.6°C
Chemotherapeutic Drug Doses	
Mechlorethamine HCl	8.0 mg
Dactinomycin	0.8 mg
Thiotepa	32.0 mg

Cosmegen[i] is one of the actinomycins, produced by various species of streptomyces. Dactinomycin is cytotoxic and concentrates in the nucleated cells producing an antineoplastic effect. The three drugs were administered in succession and circulated. Three additional boluses of these drugs were administered at fifteen minute intervals during the remainder of the thermal perfusion. After the fourth series of drug administration, the extremity was perfused for an additional 5 to 15 minutes. At the end of the perfusion, the perfusate was flushed from the venous line into waste transfusion bags and replaced with Dextran 40[h]. This was continued until the effluent was almost clear in color. In patients whose systemic hematocrit fell below 30%, homologous packed red blood cells were transfused, as indicated. The Dextran 40 was used to minimize post perfusion limb edema. Regional perfusion was then terminated. The isolation tourniquet was removed to restore physiologic circulation to the extremity. The blood vessels were decannulated, and the heparin reversed with 1.2 mg of protamine sulfate per 100 units of administered heparin.

The artery and vein were surgically repaired when necessary. The tumor was then widely excised and skin grafts performed as indicated. The patients were then transported to the recovery room for post anesthesia reversal and monitoring.

RESULTS

From March, 1988 to October, 1991 four stage III and four stage IV malignant melanomas of the extremities were treated with regional chemotherapeutic hyperthermic perfusion utilizing the triple drug therapy of mechlorethamine HCl, Thiotepa and dactinomycin. There were four males and three females with ages ranging from 23 to 71 years in this series. One upper and seven lower extremities were treated. The average BSA was 1.84 m^2 (See Table 1).

There were no deaths or complications such as arterial thrombosis, peripheral neuritis, atrophy or paralysis observed with short or long term follow up. There was no reported tissue edema of the extremity postoperatively. The response rate was 85.7 % with one patient's disease recurring. The patient was treated again with no secondary recurrence to date (25 months) (See Table 2).

Blood gases in the perfusion circuit were maintained at our targeted physiological levels with an FiO_2 range of 50-60% and sweep gas flows of .2 L/min to .4 L/min. Venous oxygen satuations were maintained at a minimum of 65%. Mean blood flow rates ranged from 700 to 1000 ml/min for the lower extremities and 250 ml/min for the upper extremity. The skin and muscle temperature maximum was 40.5°C with an average of 39.8°C for lower extremities and 38.9°C for upper extremities. The arterial blood temperature was a consistent 41.1°C. The warming time required before the first dose of chemotherapeutic drugs ranged from 20 to 35 minutes with an average time of 29.2 minutes.

Total pump time, including the warming time, averaged 81.5 minutes with a range of 69-100 minutes (see Figure 2). Venous return was generally adequate to maintain stated flow rates. There was no significant volume loss due to capillary leakage or third spacing in the limbs being perfused. The average pressure measured in the arterial line was 207 mmHg at stated flow rates and varied proportional to arterial cannula size and systemic vascular resistance. Priming volume of the perfusion

circuit averaged 840 ml. Homologous red blood cells were transfused during "washout" as clinically indicated based on the patients' systemic hematocrit.

DISCUSSION

Although the number of patients did not allow a statistical comparison with previously published data, many observations were noteworthy. The parameters met by the hyperthermic isolated limb perfusion system were consistent over a diverse patient population with varying stages of melanoma. The purpose of this review was to demonstrate safe and effective use of a compact and portable system for regional hyperthermic perfusion procedures. This was clearly demonstrated through the data.

The low complication and high response rates demonstrate the skill of the surgeons at completely isolating the extremity and the compatibility of the perfusion system to the task of isolated hyperthermic limb perfusion. The centrifugal pump minimized the chance of arterial dissection and of system failure due to over pressurization. The warming capabilities produced by the heat exchanger allowed the use of a standard water bath heater unit (maximum 42°C) blood warmer to achieve an effective range of temperatures. Some past studies were done with the water temperatures greater than 42°C presenting potential red blood cell hemolysis and denaturization of proteins (4). The membrane oxygenator provided precise control of blood gas levels in the perfusate.

Finally, it appears that this mode of treatment and the perfusion system to support it, may have an effective role in the treatment of metastatic melanoma of the extremity. The response of treatment was within our expectations as formed by previous studies (3). Although there were slight variations in the extremity temperatures, the response was consistent throughout the different regions of the extremity. Further testing on a larger patient population is recommended to statistically prove that a more compact, portable perfusion system will successfully produce safe and effective treatment parameters for selected melanomas of the extremities.

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