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CAN PERSONALIZED TOURNIQUET SYSTEMS PREVENT CHEMOTHERAPY-INDUCED ALOPECIA?

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INTRODUCTION

Alopecia (hair loss) is a common consequence of cancer treatment known to have a profound impact on quality of life. Various strategies for improving quality of life by preventing chemotherapy-induced alopecia (CIA) have been investigated. From the mid-1960s to early 1980s, tourniquet technologies were investigated as a means of stopping the penetration of arterial blood containing chemotherapeutic agents into the scalp and hair follicles [1-5]; their ambiguous results precluded incorporation into any standard of treatment.

The tourniquet technologies and settings used in such early investigations are now considered to be unsafe, ineffective and obsolete [6]. Their use likely allowed arterial penetration of agents in many instances and excessive pain leading to discontinuation in others, e.g. tourniquet pressures could not be set optimally relative to a patient's personalized scalp occlusion pressure and instead were set arbitrarily or erroneously based on SBP; accuracy and reliability of mechanical pressure regulation was poor; and limb tourniquet cuffs would not apply pressure safely and uniformly around the scalp.

Our hypothesis is that fundamental advances inherent in personalized tourniquet systems developed within our group over 38 years enables the optimal, safe, comfortable and reliable stoppage of penetration of arterial blood into the scalp during infusion of chemotherapeutic agents, which can enable the prevention of alopecia and improve quality of life. This paper describes these advances, and presents options for integrating various treatment protocols involving modern chemotherapeutic agents having differing pharmacokinetics. The paper also discusses key clinical aspects associated with clinical studies and usage of personalized scalp tourniquets for preventing CIA. Personalized tourniquet systems may significantly improve quality of life by safely stopping penetration of arterial blood flow into the scalp during chemotherapy, with low treatment cost and low impact on treatment times and workflow.

SAFETY

Surgical tourniquets:

Surgical tourniquets are commonly set at pressures ranging between 100-250 mmHg for upper limb surgeries and 150-350 mmHg for lower limb surgeries [7]. On modern tourniquet instruments, users can set maximum tourniquet times ranging between 0-240 minutes, and for certain surgical procedures that time limit can be extended substantially, at the discretion of surgical staff [7]. New personalized tourniquet systems allow tourniquet pressures to be substantially lowered to optimal levels that are both safe and effective [8] for operative and perioperative applications. Based on preliminary tests we have completed on normal subjects, personalized scalp tourniquet pressure levels are substantially lower than personalized pressure levels used for limb surgeries, and are in the range of 90-140 mmHg. Additionally, for preventing CIA, scalp tourniquet time is anticipated to be substantially less than the maximum standard time limits in surgical tourniquet systems.

Personalized tourniquet concepts of DOP and PTP:

Distal Occlusion Pressure (DOP):

DOP is the minimum pressure required, at a specific time in a specific tourniquet cuff applied to a specific patient's limb at a specific location, to stop the flow of arterial blood distal to the cuff.

For scalp tourniquets, DOP is affected by variables including the elevation of the head relative to the heart, snugness and consistency of tourniquet cuff application to the head, characteristics of the selected tourniquet cuff, cuff width-to-head-circumference ratio, hair volume and length beneath the cuff, scalp muscle tone and muscle tension, presence and type of scalp protection sleeve, and physiologic characteristics of the patient including systolic blood pressure, head temperature, and vascular health.

Personalized Tourniquet Pressure (PTP):

The PTP is a patient specific tourniquet pressure used to stop blood flow past the cuff during treatment. It is a function of the DOP and includes a margin of safety to account for physiological variations during treatment. In successive-treatment chemotherapy applications, DOP should be measured prior to the start of each treatment. The personalized tourniquet system then determines the PTP based on the DOP. Figure 1 depicts the personalized tourniquet system applied to a patient. The underlying technology is described in detail elsewhere [9]. A YouTube link illustrating clinical use of the personalized tourniquet system for establishing and maintaining PTP is available at https://youtu.be/AVn5ayNAQmk

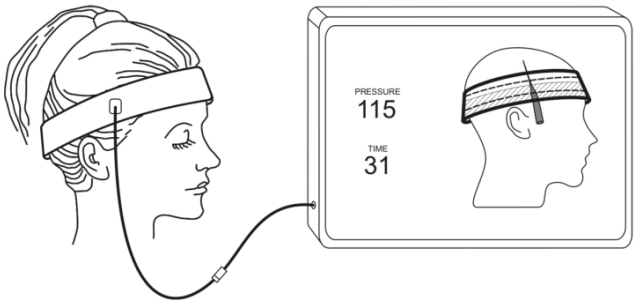


Figure 1. Personalized tourniquet system, with cuff applied to patient scalp and instrument displaying applied cuff pressure and inflation time.

Previously reported usages of scalp tourniquets

Pneumatic tourniquets have been used on the scalp for over 111 years, with no reported injuries. The first use of a pneumatic scalp tourniquet was reported by Harvey Cushing in 1904 as an advance over earlier non-pneumatic tourniquets [10]. He conducted 18 craniotomies with the benefit of a pneumatic tourniquet and reported no ischemic injuries distal to the cuff, no nerve injuries and no soft tissue injuries. While Cushing did not report the specific tourniquet times involved, the typical time required for craniotomies ranges from one hour to several hours. It is worth noting that Cushing had no means to minimize tourniquet pressure by establishing and maintaining a personalized minimum tourniquet pressure based on DOP, and so the tourniquet pressures used would have been substantially greater than the minimum needed to be safe and effective.

From the mid-1960s to mid-1980s pneumatic tourniquets were investigated as a means of preventing or minimizing alopecia [1-5]. These reports involved small numbers of patients, and tourniquet technologies at that time did not permit accurate determination of optimal tourniquet occlusion pressure based on DOP and were not able to accurately and reliably maintain any specified pressure level. The tourniquet technologies and settings used in such early investigations are now considered to be unsafe, ineffective and obsolete [6,7]. Their use likely allowed arterial penetration of agents in many instances and excessive pain leading to discontinuation in others, eg tourniquet pressures could not be set optimally relative to a patient's personalized DOP and instead were set arbitrarily or erroneously based on systolic blood pressure (SBP); accuracy and reliability of mechanical pressure regulation was poor; and limb tourniquet cuffs would not apply pressure safely and uniformly around the scalp. Despite these and other flaws in the reported methodologies, no tourniquet-related patient injuries were reported in these studies [11].

Cold caps for the prevention of alopecia in adjuvant chemotherapy

More recently, cold caps have been used in an effort to stop arterial blood flow at hair follicles by cooling the scalp [12]. In comparison to personalized tourniquet technology for preventing CIA, cooling technology is substantially more expensive and cumbersome, and has a more significant impact on clinic configuration, clinic workflow and time. Reported outcomes involving the use of cold caps have been mixed, but typical times during which the scalp was presumably ischemic in the region of hair follicles ranged from 2 hours to over 5 hours [13]. There have been no reported ischemic injuries to the scalp and no reported nerve or soft tissue injuries resulting from cold caps for periods of time that are substantially longer than the tourniquet times anticipated for clinical use of personalized scalp tourniquets. This is because the cold cap technique requires that the scalp be cooled for a substantial period of time prior to administration of the agents, unlike the tourniquet technique.

Scalp nerves, applied pressures and pressure gradients

As noted above, no pressure-related nerve injuries have been reported due to any previous use of scalp tourniquets. Additionally, in a common technique of hair restoration [14], intentionally severed nerves completely regenerate within a period of weeks, restoring normal nerve function. Thus, even in the improbable event that a scalp nerve is injured as a result of directly applied pressure and pressure gradients, any such injury is anticipated to be minor and temporary.

Maximum safe duration of scalp ischemia

The question of the maximum safe duration of scalp ischemia is best answered by a critical review of recent literature on successful scalp replantation after total scalp avulsion [15-16]. A recent case report from Canada is especially illustrative, noting full return of hair growth in undamaged scalp areas after replantation of a total avulsed

scalp with a scalp ischemic time of 9.1 hours [15]. Overall, if a totally avulsed scalp is intact and undamaged, the literature indicates that replantation can be successful, with full return of hair growth in undamaged areas, after warm scalp ischemic times between 3-24 hours, with a mean duration of 10.1 hours [16].

CLINICAL EFFECTIVENESS

Key variables to consider in evaluating and improving the effectiveness of personalized tourniquet systems in preventing CIA are summarized below. A small initial 'proof of principle' clinical study involving a small number of patients and two treatment protocols is planned, and additional studies are envisioned to include: various treatment protocols; different single or multiple chemotherapeutic agents; varying infusion durations and concentrations; and variations of personalized tourniquet parameters such as tourniquet onset and duration relative to infusion onset and duration.

Choice of chemotherapeutic agent

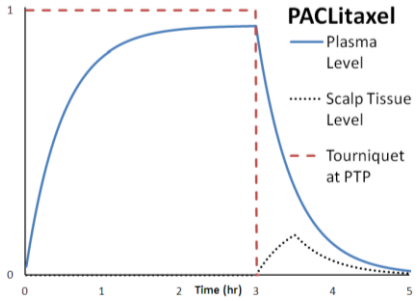
We hypothesize that the ideal treatment protocol will employ a single chemotherapeutic agent having a very short distribution half-life, administered by intravenous infusion over a short time period, wherein a personalized tourniquet system will maintain a Personalized Tourniquet Pressure (PTP) during the infusion and for a period of time thereafter related to the distribution half-life and the elimination half-life.

Figure 2 summarizes the relevant half-life properties of agents commonly used in adjuvant breast cancer chemotherapy protocols and for each agent depicts the predicted effectiveness of a personalized scalp tourniquet maintained at a patient's PTP for differing periods of time. Distribution half-life corresponds to the time required for a 50 percent reduction in the concentration of the agent circulating in the plasma volume (after infusion or oral administration) due to distribution of the agent from the plasma into body tissues. Elimination half-life corresponds to the time required in an elimination (late) phase for plasma concentration of the agent to decrease by 50 percent due to elimination of the agent from the body. During the distribution phase, changes in the concentration of the agent in plasma reflect primarily movement of drug within, rather than loss from, the body. Once the agent in plasma and tissues has reached equilibrium, during the elimination phase, the decline of plasma concentration is driven by elimination of the agent from the body.

Agent: PACLitaxel

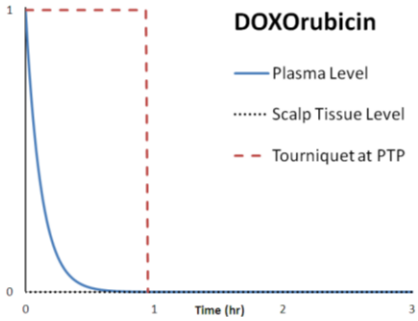
Alopecia Prob.: 87-93 %
Dist. Half-life: 20.4 min
Elim Half-life: 10 hrs*
Infusion time: 3-hrs

** varies with dose and infusion time*



Agent: DOXOrubicin

Alopecia Prob.: 100%
Dist. Half-life: 5min
Elim Half-life: 35-54hrs
Infusion time: 1-hr



Agent: Cyclophosphamide

Alopecia Prob.: 40-60%
Dist. Half-life: 2-3 hrs+
Elim Half-life: 1.8-12.4hrs
Infusion time: 20-60min

+*time to peak Concentration*

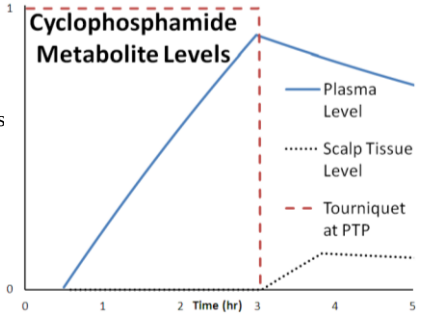


Figure 2 Predicted effectiveness of a personalized scalp tourniquet at PTP during infusion of commonly used chemotherapy agents causing CIA.

Patient Tolerability and Mitigation of Discomfort

Chemotherapy patients are conscious and aware, unlike surgical patients, and thus some patients may experience an uncomfortable sensation of pressure on the head. Demonstration applications of the personalized tourniquet system to the scalp of 10 normal subjects for periods between 20-40 min indicated that the need for sedation and analgesia should be minimal. However, clinical studies and usage may involve tourniquet times of 3 hr or more. Also, it is recognized that patients are dealing concurrently with the implications of a devastating diagnosis, the response to which may vary greatly among individuals and thus may have a major impact on anxiolytic/analgesic requirements.

With these considerations in mind, an analgesic protocol has been established to improve tolerability and mitigate discomfort.

Assessment of chemotherapy-induced alopecia (CIA)

A unique aspect of any clinical study or use involving personalized tourniquets is that each patient might serve as her own control, allowing relative CIA to be assessed above and below the proximal tourniquet edge.

During a clinical study, relative CIA will be assessed subjectively on a 0-5 likert scale by the patient, by an oncology nurse, and by a medical oncologist. In addition, CIA will be assessed objectively by expert evaluation of standardized photographs.

Impact on Clinical Workflow

In studying the use of personalized tourniquet systems to prevent CIA, it is important to assess relative impacts on clinic workflow, and to adapt clinical procedures to minimize any such impacts. A comparison of tourniquet-related impacts to those associated with scalp cooling technologies may be instructive because, in addition to potentially greater effectiveness at lower cost, personalized tourniquet systems will likely require relatively less time for patient preparation, less clinic space for storage and use, less clinic reconfiguration, and may be substantially less time-consuming and less cumbersome for clinic staff to operate.

Impact on Patient and Quality of Life

The immediate impact from a patient perspective relates to patient tolerability, the impact of medications to reduce any patient discomfort, anxiety and sensation of applied pressure, and factors relating to any patient discontinuing treatment, with a view to mitigation.

More fundamentally, there is a need to assess the impact of prevention or reduction of CIA on the extent to which it improves a patient's sense of personal health and wellbeing during and after chemotherapy. This is best done through the use of accepted, standardized methods for assessing health-related quality of life.

Additionally, from a nursing and clinic perspective, orientation of patients and staff, cuff application and system operation, and any additional documentation requirements, will all impact the work satisfaction of staff to varying extents to be determined.

DISCUSSION AND CONCLUSION

Personalized tourniquet systems are optimally effective in minimizing tourniquet pressure while assuring full stoppage of arterial flow distal to the tourniquet cuff.

The advances in personalized tourniquet systems described above have the potential to significantly improve quality of life by safely stopping penetration of arterial blood flow into the scalp during chemotherapy, with low treatment cost and low impact on treatment times and workflow.

CONFLICT OF INTEREST

F. Howard, S. Abadi and C. Simmons have no conflicts of interest related to the subject matter. J. McEwen, M. Jameson and J. Jeyasurya have financial interests in companies that develop tourniquets.

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