Safety of Naturopathic Infusion Therapy: A 12-Month Quality Assurance Study

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Introduction

Naturopathic Medicine (NM) is a comprehensive primary care profession that provides important health care delivery to patients in several regulated jurisdictions in North America (Table 1). An emerging sub specialty within the field of NM is Naturopathic Infusion Therapy (NIT). This involves the administration of various substances consistent with naturopathic practice intravenously to patients. Substances administered in this manner include: vitamins and minerals, amino acids, botanicals, immune agents, chelating agents and anesthetics. Within the province of Ontario, where this quality assurance patient record review study was conducted, there are extensive training and continuing education requirements to become certified and maintain certification to perform NIT. Since the initiation of the naturopathic parenteral therapy policy in Ontario in 2004 the number of practitioners in the province practicing NIT have grown to 192. While there have been several studies analyzing the safety and rates of complication in convention infusion therapy, no studies exist in the field of NM. Given the increasing usage of naturopathic medicine and the increased number of practitioners performing this therapeutic modality it is important to know the safety profile of NIT. One recent article attributed a severe reaction to a "naturopathic infusion" it is unknown whether the practitioner responsible for administering this treatment was a licensed naturopathic doctor who was trained to perform such a procedure. [i] Clearly, given the increased interest and demand for NIT, there is a need to validate the safety of these treatments. The goal of this study is to review the rates of complications related to the procedure and rates of adverse reactions to the substances being administered in a typical outpatient setting performing NIT, and to compare that with published rates in a conventional setting.

Licensed States	Licensed Provinces
Alaska	British Columbia
Arizona	Manitoba
California	Ontario
Connecticut	Saskatchewan
District of Columbia	
Hawaii	
Idaho	
Kansas	
Maine	
Minnesota	
Montana	
New Hampshire	
North Dakota	
Oregon	
Utah	
Vermont	
Washington	
United States Territories: Puerto Rico and Virgin Islands	

Table 1: Regulated jurisdictions for naturopathic doctors in North America. Source American Association of Naturopathic Physicians and Canadian Association of Naturopathic Doctors

Method

This study was a patient record review over a 12-month period from June 1, 2010 – May 31, 2011. All NIT treatments during this time were compiled by reviewing scheduling and billing information for the centre. Treatments were recorded in an electronic heath record (EHR) system. Patient data collected at each treatment visit are listed in Table 2.

Table 2: Data included in each treatment record
• Patient Name • Date and time of the initiation and discontinuation of treatment • Exact composition of infused solution • Osmolarity calculation of infusion • Venous access device used including gauge • Anatomical location of venous access • Number of attempts to establish venous access • Drip rate • Pre and post vitals (Including: heart rate (HR), blood pressure (BP), respiratory rate (RR), oxygen saturation(PO)) • Any complication or reaction experienced, intervention applied and response to intervention • Status of device on removal • Status of site on removal (including presence and grading of phlebitis or infiltration)

Follow up visits were also reviewed to assess any late onset complications or reactions. Data collectors compiled information from each record and including patient's vitals, treatment complications and adverse reactions. Figure 1 lists the primary indication for NIT for patients in this study.

Changes in vitals (HR, BP, pulse oximetry) for each patient treatment were recorded and the mean calculated. Any complications or adverse reactions were analyzed by the study investigators to assess causality and to classify. In this study we used the Infusion Nursing Society standards for treatment related complications classification and grading, and Cancer Therapy Evaluation Program: **Common Terminology Criteria for Adverse Events v3.0 (CTCAE)** to evaluate and classify adverse reactions observed. Figure 2 lists the inclusion and exclusion criteria for treatments records developed prior to undertaking the case review.

A total of 1601 treatments procedures were recorded during the study period. 93 treatment procedure records had some form of documentation regarding patient vitals missing and were excluded. No other exclusions were made. Complication and adverse reaction rates for the excluded treatments were reviewed and comments will be made in the results section. In this study an NIT treatment procedure refers to one infusion session. During a single session more than one treatment may have been applied.

Vitals were analyzed to determine if there was any significant changes post treatment. The mean change for BP, HR, RR, and PO all treatments (pre and post) was calculated and checked for significance.

Treatments were administered according to the facilities protocols that include standards for frequency of administration, dose escalation, maintenance dosage, and dose modifications when intolerance is encountered. The following are summaries of our treatment protocols:

High Dose Ascorbic Acid

Ascorbic Acid (AA) has an important role in tissue and wound healing through its support of collagen synthesis, modulation of immune reactions and reduction in inflammation. Recently, AA

has also shown promise in pre-clinical research as a potential additive therapy in cancer. High doses of AA have been shown to induce the production of H2O2 in tissues leading to selective tumoral cytotoxicity[ii, iii], down regulate gene expression involved in angiogenesis,[iv, v] and reduce expression of matrix metalloproteases involved in invasive behavior[vi]. AA is transported in the gastrointestinal tract in an energy dependent process that becomes saturated at increasing oral doses.[vii] In order to achieve clinically relevant doses for cancer and immune activation, infusions are required. [viii]

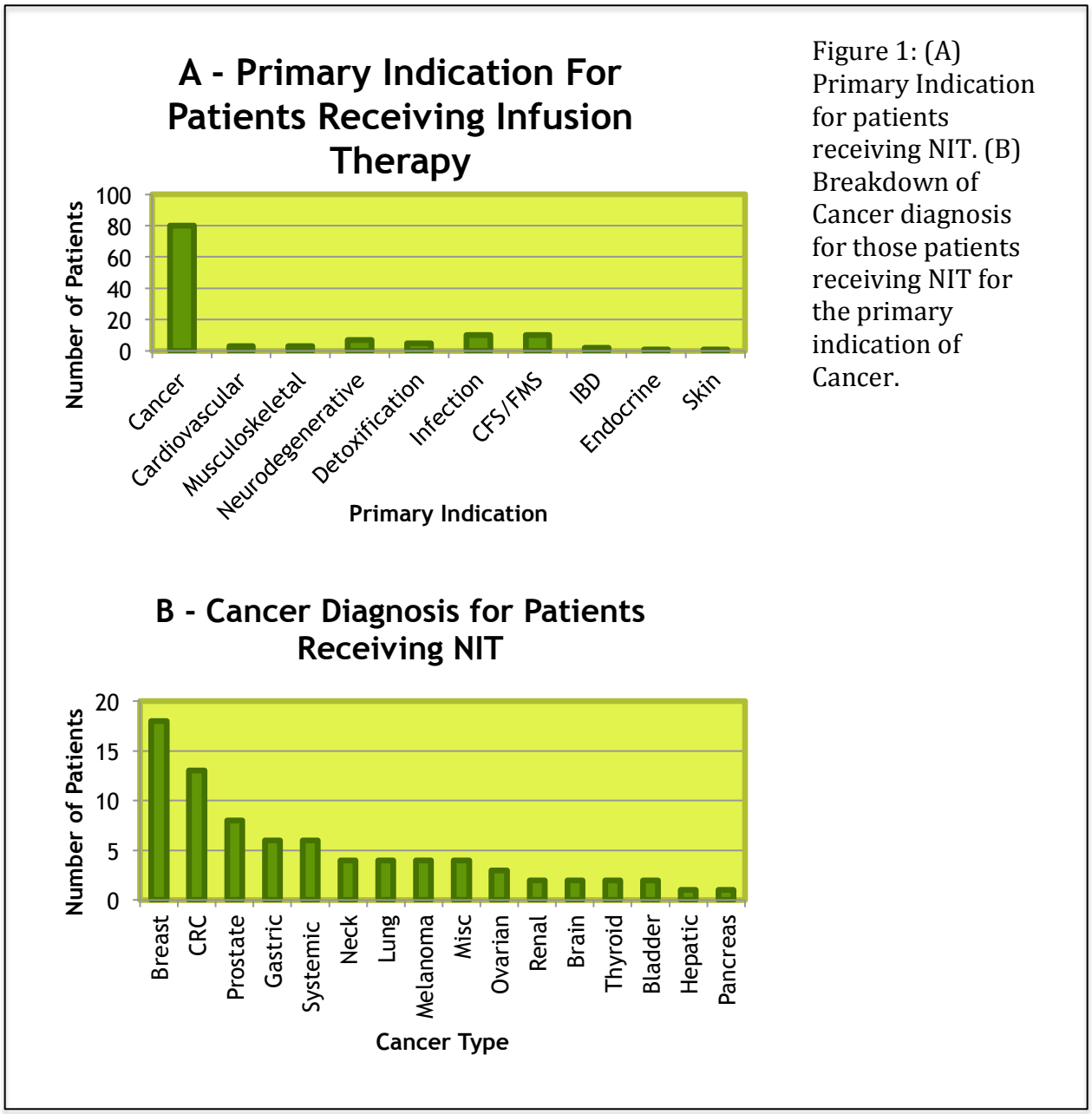

Figure 1: (A) Primary Indication for patients receiving NIT. (B) Breakdown of Cancer diagnosis for those patients receiving NIT for the primary indication of Cancer.

Figure 2: Inclusion/exclusion criteria adopted to

Inclusion

- Patients received infusion therapy from June 1, 2010 and May 31, 2011
- Patient has had at least one follow-up visit post infusion treatment where complications can be reviewed either in person or via phone

Exclusion

- Vitals documentation on treatment sheet for pre post (BP, HR, PO) missing
- No follow up visit post treatment (Patient Lost)
- Lack of identified equipment used in infusion
- No documentation of indication for infusion therapy
- No documentation of presence or lack of indicated comorbidities in file

Our clinic dosing protocol for AA involves starting doses of 10 g and escalating by 10-15 g until maintenance dosage is established or until patient experiences an adverse/intolerance reaction. Since AA administered in high doses can lead to severe hemolytic anemia in individuals with G6PD deficiency, all patients are screened for this deficiency prior to dose escalation. Patient's whose eGFR was below 60 at initiation of treatment had dose escalations at 5 g per treatment until maintenance dose was reached. The maintenance dosing of AA at our centre varies depending on the indication for use. If the treatment indication is for tissue and wound healing and immune activation maintenance dose will range from 25-50 g administered over .75 – 1.5 hours. If the treatment indication is for supportive care during cancer treatment the maintenance dose is calculated at 1.5 g per kg. This is a dose determined by Hoffer and colleagues in a recent phase I trial to achieve serum levels consistent with levels found in pre-clinical studies to produce a cytotoxic effect on malignant cells. The frequency of AA treatments ranged from 1-3 times weekly. [ix]

European Mistletoe (Viscum Album)

European mistltetoe or Viscum album VA has a long history of use in parenteral form as a supportive cancer treatment since it was first applied to Leukemia patients in 1916. The therapeutic used in this study was Helixor which is a fresh aqueous extract of VA. VA is normally applied as a supportive treatment for cancer patients via sub cutaneous route. In this manner it has been shown to exhibit immune enhancing effects and positive neuroendocrine effects leading to clinical improvements in conventional cancer treatment tolerance and quality of life. Tumor tissue assays and pre-clinical animal studies validate the effect of mistletoe lectins (ML) as primary cytotoxic agents in many cancer entities. The ML amounts contained in VA preparations vary, but generally occur in mcg or nanogram quantities. In order to achieve clinically cytotoxic dosing of MLs local administration or high dose systemic administration through infusion is necessary. Due to the potential for serious allergenic effects of mistletoe patients are first challenged with .1 mg of VA intradermally and the site is observed for 24 hours for indication of severe allergic reaction. If no reaction occurs, patients begin with 50-100 mg of the preparation

delivered alone in 0.9% sodium chloride or in combination with AA over a period of 2-4 hours. The does for each patient was increased at each subsequent treatment by 100 mg until an intolerance reaction is reached or a maximum dose of 1,000 mg. Intolerance reactions with VA infusion treatments are related to overactive immune induction and the development of a cytokine release syndrome (CRS). This is recorded as an ADR and treatment is stopped. Subsequent treatments are continued at a dose reduction of 200-400 mg or until tolerance is established. Treatments are administered 2-3 times weekly.

Sodium Bicarbonate

Sodium bicarbonate (SB) infusions are generally administered as part of treatments for episodes of acute acidosis or are added to infusions for the purposes of buffering acidic admixture ingredients. Pre-clinical and animal research exists on the potential role of SB in cancer treatment by reducing invasive behavior and improving immune activity directed at solid tumors.[x, xi, xii] A study by Hoang and colleagues showed a positive pain relief using infusions of SB in a palliative prostate care setting.[xiii] In this study, patients receiving this treatment are started at 1% SB in a 500 mL infusion delivered over 3-6 hours. Treatments are delivered daily, one-week on and one-week break. For the first week the treatment dose was escalated daily by 1% per treatment until the 5% maintenance dosage was achieved or until intolerance reaction was experienced. If a patient has tolerance issues the dose is reduced to the last tolerated dose for future treatments. This cycle is repeated up to 10 times.

Glycyrrhizic Acid

Glycyrrhizic Acid (GZA) infusions have primarily been employed in chronic viral hepatitis for hepatoprotection[xiv] and prevention of hepatocellular carcinoma.[xv] Research on GZA shows promise for other viral conditions like HIV[xvi], CMV, EBV[xvii] and as a general liver supportive therapy. GZA has a known potential for the development of pseudoaldosteronism resulting from its inhibition of the adrenal enzyme 11 **β** hydroxysteroid dehydrogenase 2.[xviii,] This reaction normally occurs from GZA accumulation with chronic over ingestion or in clinical trials with GZA that administered treatments daily. .[xix, xx] In this study patients who were administered GZA were given concurrently with AA infusion treatment administered either 1-2 times weekly. Treatment was started at 80 mg and then increased by 80 mg each subsequent treatment until between 240 and 300 mg. This dosage corresponds to clinical trial dosages in GZA that have good tolerance and clinical effects.

Myer's Cocktail

The Myer's Cocktail is named after John Myers, MD the physician first credited for administering the treatment. This infusion treatment is a general label given to short infusions or IV pushes that contain b vitamins, ascorbic acid, magnesium, and calcium. Other vitamins, minerals or cofactors can be added to this mixture. While it commonly used in integrative care settings for fatigue and pain syndromes there is only one case control study published on its safety and efficacy.[xxi] In our study patients received a standard formula along with various additions that are shown in table 2. Treatments were given 1-2 times weekly generally for short 2-4 week periods.

Ingredient	Quantity
Magnesium Sulfate	500 – 2,000 mg
Calcium Chloride	100 – 1,000 mg
Ascorbic Acid	1,000 – 5,000 mg
B Complex 100	1-3 mL
Pyridoxine	50-500 mg
Dexapanthenol	100-300 mg
Hydroxycobalamin	1,000 mcg – 5,000 mcg
Selenium	40 mcg – 200 mcg
Hydrochloric Acid 1:500	5-10 mL

Malnutrition Formulations

These infusion formulas consist of vitamins, minerals, trace elements and amino acids and are delivered in Normal Saline (NS), Lactated Ringers (LR) or 5% dextrose (D5W). Malnutrition formulations were most often given to cancer patients or patients with inflammatory bowel disease to support patient's nutritional status due to inadequant intake or malabsorption. Patient's receiving these infusions we able to consume foods either by mouth or through medical apparatuses like a G or J tubes. Dosage of therapeutics and frequency of administration was determined on an individual basis ranging from one to three treatments weekly.

Results

Changes in Vitals

Given the rapid administration of hypertonic solutions in NIT we hypothesized that there would be significant differences in pre treatment and post treatment vitals. Patients receiving NIT did indeed experience an increase in both systolic and diastolic blood pressure by 6.6% ($p < 0.01$) and 5.5% ($p<0.01$) respectively. We observed that mean Heart Rate was reduced post treatment 3.2% ($p<0.05$). There were no significant changes in pulse oximetry post NIT treatments observed.

Complications

There were no serious complications during the study period. The only complications recorded were infiltration and phlebitis. A total of 12 infiltrations were observed during the study period (8 grade 1 and 4 grade 2). This translated to an infiltration rate of 0.8%. There was a total of 5 phlebitis recorded during the study period (4 grade 1 and 1 grade 2). 4 of the 5 reported phlebitis' were experienced in patients receiving sodium bicarbonate infusions. Total phlebitis rate was 0.3%.

ADRs

During the study period there was a total of 49 ADRs. Table ** breaks down the classification and severity of ADRs over the study period. The most common ADR (12) was cytokine release syndrome (CRS) caused by infusion of VA extracts. These reactions consisted of mainly of

generalized uritcaria and angioedema. Only 2 patients required treatment for the CRS that resulted in angioedema. Treatment for these patients consisted of oral diphenhydramine, resulted in immediate symptom resolution, and no patient required hospitalization or further treatment. The second most common ADR (10) was transient hypertension greater than 20 mmHg lasting for several hours post treatment. These patients required not treatment interventions and showed normalized blood pressure on follow-up.

Table shows ADR's by treatment type and gives the ADR rate for each treatment over the study period. The treatment with the highest ADR rate during this study period was intravenous infusions of sodium bicarbonate. ADR rate in this category was 12%. In addition, the phlebitis rate in this group was much higher (4 out of 124 treatments 3.2%).

Table Adverse Drug Reactions Listed By CTCAE System and Grading		
Reaction	Grade I	Grade II
Constitutional Symptoms		
Fatigue	2	0
Thirst	1	0
Cardiac Symptoms		
Hypertension	10	0
Chest Pain	2	0
Palpitation	1	0
Syndromes		
Cytokine Release Syndrome	10	2
Pain		
Headache	6	
pain at insertion site not related to phlebitis	0	2
Gastrointestinal		
Nausea	5	0
Pulmonary/Upper Respiratory		
Feeling of tightness in chest/Mild dyspnea	3	1
Cough	1	0
Hemorrhage and Bleeding		
Nose bleeding	2	0
Neurology		
Parasthesia hands and feet	1	0
Total	44	5

Table ADR Totals by Treatment Type

Treatment Type	ADR and (# patients reporting)	Number of treatments*	ADR Rate

Ascorbic Acid	24**	1042	2.3%
Glycrrhyzic Acid	0	75	0%
Malnutrition	2**	79	2.5%
Meyer's	0	22	0%
Miscellaneous	0	154	0%
Sodium Bicarbonate	12	124	10.5%
Viscum Album	12	422	2.8%

* Total number of treatments for each modality exceeds the total number of treatment procedures listed in the study as a patient may have received more than one treatment during a single treatment procedure

** One of the ADR for these treatments was counted twice since the patient received both high Dose AA and Malnutrition infusions and causality good not be delineated unequivocally for either

Discussion

NIT is an emerging subspecialty field within naturopathic medical practice. Until this study there has not been an evaluation of the safety of this practice. In our retrospective case file review quality assurance study we reviewed the safety of NIT within the context of an outpatient community based practice. NIT treatments most often involve the relatively rapid administration of hypertonic solutions. We found that patients receiving these treatments had an average increase in systolic blood pressure of 6.6% and an average increase in diastolic blood pressure of 5.5%. Blood pressures returned to pretreatment values in patients who had a greater than 20 mm Hg rise in systolic blood pressure within hours of the termination of treatment. In addition, none of the patients showed a trend to an increased blood pressure over the duration of the study. This is an important factor to consider when administering these solutions as this likely NIT treatment induced intravascular expansion could lead to circulatory overload. In this study patients were carefully evaluated to determine the risk of circulatory overload and steps were take to prevent this from occurring. An interesting finding in this study was the overall slight (3.3%) but statistically reduction in heart rate. Most of the NIT treatments administered in this study contained magnesium sulfate (MgSO4). It has been documented in prior studies that MgSO4 can lead to a reduction in heart rate.[xxii, xxiii] It is not unreasonable to assume that this is the cause of observed mild heart rate reduction.

We reviewed complications and adverse reactions in 1508 treatment procedures. The complications observed in this study were phlebitis and infiltration. There were no serious treatment related complications during this study. The main complications observed were infiltration and phlebitis. The infiltration and phlebitis rate found during the study period were 0.8% and 0.3% respectively. This compares favorably to studies involving infusion practices within institutional settings performed by nurses. Chukraev described rates of infiltration in a conventional hospital nursing setting to be 5.69%. [xxiv] In a short term prospective trial by Palefski and Stoddard within a hospital setting infiltration rates were found to be 7.5% in treatments performed by infusion specialist nurses and 13.9% in treatments performed by general nurses. The same study found phlebitis rates of 2.5% when procedures we performed by infusion nurse specialists and 4.9% when performed by general nurses.[xxv] There are two key factors that lead to the lower rates of phlebitis and infiltration observed in our study. The first is that dwell times of

the peripheral catheters were generally for no longer than 1 day. Previous studies have shown a sharp increase in both phlebitis and infiltration rates past 2 days of catheter dwell time.[xxvi, xxvii] The second factor is that naturopathic doctors performing this treatment have undergone significant training and continuing education to ensure safe administration, a practice requirement for the jurisdiction of the study.

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