2012 대한임상건강증진학회 춘계 통합학술대회 / 연수강좌

Intravenous (Micro)nutrient Therapy
– 피로 중심으로 –

아주대병원 가정의학교실
김광민

Intravenous Nutritional Therapy

- A treatment method, which uses vitamins and minerals and administers these directly into the bloodstream.

Contents

- History and rationale for IV therapy
- Therapeutic application for IVNT
- Fluid balance assessment(osmolarity)
- Complications of IV therapy
- Pharmacology of IV vitamins and minerals

History and IVNT (History of Myers' Cocktail)

- John Myers – a physician from Baltimore
- Myers did not leave any published or print material on the composition of the IV treatment
- Myers used a 10-mL syringe and administered by slow IV push
- Current formulations have been modified to by Dr. Alan Gaby who took over care of Dr Myers' patients after his death in 1984

The Myers' Cocktail

- Myers' Cocktail Composition-

Magnesium chloride hexahydrate (20%)	5 ml
Calcium gluconate (10%)	3 ml
Hydroxocobalamin (1,000 mcg/ml)	1 ml
Pyridoxine hydrochloride (100 mg/ml)	1 ml
Dexpanthenol (250 mg/ml)	1 ml
B-complex 100*	1 ml
Vitamin C (500 mg/ml)	5 ml
Sterile Water	20 ml

B-Complex 100 of The Myers' Cocktail

- B-Complex 100 contains the following per each ml:

• Thiamine HCl	100mg
• Riboflavin	2mg
• Pyridoxine HCl	2mg
• Panthenol	2mg
• Niacinamide	100mg
• Benxyl Alcolhol	2%

Rationale for IV therapy

1. Direct cellular nutrition By avoiding any alteration in the nutrients, which may occur from the actions of digestive enzymes
2. Higher intra- and extracellular concentration of nutrients than can oral supplementation any dose.
3. Immediate therapeutic effects
4. INVT will alleviate nutritional deficiencies

Theoretical Basis for IVNT

- Intravenous administration of nutrients can **achieve serum concentrations** not obtainable with oral, or even intramuscular administration.
- Viitamin C concentration according to Routes

Administration	Serum concentration
Oral, 200mg/day	1.2mg/dL
Oral, 2500mg/day	1.5mg/dL
Oral, highest concentration	9.3mg/dL
IV 50g/day	80mg/dL

Theoretical Basis for IV Nutrient Therapy

- Various nutrients have been shown to exert **pharmacological effects, which are in many cases dependent on the concentration** of the nutrient.
- For example, an antiviral effect of vitamin C has been demonstrated at a concentration of 10-15 mg/dL, a level achievable with IV but not oral therapy

Theoretical Basis for IVNT

- **Correcting Intracellular Nutrient Deficits**
- Higher intracellular nutrient concentration necessary in some cases to maintain proper cellular function
- E.g. Magnesium concentration 10 times higher in myocardial cells as compared to extra-cellular concentrations
- Magnesium ions promote relaxation of both vascular and bronchial smooth muscle – effects that might be useful in the acute treatment of vasospastic angina and bronchial asthma, respectively.

Therapeutic Applications of IVMT

- Fatigue (including chronic fatigue syndrome)
- Fibromyalgia
- Chemical toxicity
- Asthma
- Migraines
- Acute muscle spasm
- Upper respiratory tract infections
- Chronic sinusitis
- Seasonal allergic rhinitis
- Cardiovascular disease
- Depression
- Narcotic withdrawal
- Chronic urticaria

Common Ix of IVNT

- Patients who feel generally "unwell" for any number of reasons
- Chronic fatigue syndrome including adrenal fatigue
- Fibromyalgia
- Asthma
- Migraines
- Acute muscle spasm
- Chemical toxicity secondary to any acute, chronic or intermittent exposure to chemicals

Containdications

- Allergy to a nutrients; impossible
- Severe red cell fragility disorders that present a theoretical risk with hypotonic solutions
  - Thalassemia Major
  - Sickle cell anemia
  - G6PD deficiency

IVNT 주의사항

- 정상 혈액 osmolarity 275-308 mOsm
- 비타민 B12는 빠르게 소변으로 배설되어 IM 선호
- Glutathione 및 아미노산 제제는 IVNT(비타민 C)와 분리하여 정주

General Caveats

- Use only preservative-free nutrients
- Use IV solutions only in glass – never in plastic bags
- Never give trace minerals via IV "Push"
- Use a "primer" IV before you give an IV with trace minerals
- Observe the rules for safe osmolarity

Osmolarity

- Osmolarity (Osm) ;
  - the number of osmoles (Osm) of solute per liter (L) of solution
  = Osmoles / Volume
- mOsm/L = Milliosmoles / Liter
- mOsm/mL = Milliosmoles / Milliliter

Calculating Osmolarity for all IVs

- Plasma Osmolarity
  – 0.280 ~ 0.310 mOsm/ml or 280 ~ 310 mOsm/L
- Most IVs are slightly to moderately hypertonic.
- Hypotonic IVs can be dangerous.

Safe Osmolarity Limits

- IV Infusion (mOsm/ml)
  - Large vein 1.20
  - Medium vein 0.700
  - Any vein 0.400
- The longer the infusion and the smaller the vein, the more conservative you should be with the osmolarity

Osmolarity

Formula	mOsm/ml	cc	total mOsm
Beecom	2.14	2	4.28
Bivon	2	8	16
Dutenol	1.36	2	2.72
Thiamine	0.92	2	1.84
Mega-C	5.94	20	118.8
Kyominotin	0.29	40	11.6
Bidoxin	1.5	1	1.5
Magnesium	0.8	20	16
5% DW	0.25	200	50
Total		295	222.74

Calculating osmolarity

- (Total mOsm of addives/0.310) - total volume of additives = ml of water to add
- Ex) 172.74mOsm, 95cc of additives
  (172.74 / 0.310) - 95 = 465.23 cc

Adverse reactions of IVNT

1. Sensation of heat
   - large doses or rapid administration
   - d/t primarily Mg
   - typically begins in the chest
2. . Vasovagal reactions
   - Too rapid administration of Mg
   - lightheadedness or even syncope
   - Mg용량 줄여야

Adverse reactions of IVNT

3. Anaphylxis - theoretically possible
   d/t nonspecific release of histamine
   Myers' < I.V thiamine
   thiamine supplementation in the presence of Mg def.
   increase the severity of the Mg deficiency
   Mg deficiency -→ spontaneous release of histamine
   increase the incidence of experimentally induced anaphylaxis in animals
   So, Mg in the Myers' reduce the risk of an anaphylactic reaction to thiamine

The difference between vasovagal and anaphylactic reactions

- Vasovagal
  - Pallor
  - Cold, clammy feel and look
  - Slow pulse with low BP
- Anaphylactic
  - Redness of eyes and often skin
  - Anxiety, sometimes with flushing
  - Rapid pulse with falling BP

Adverse reactions of IVNT

4. Phlebitis at the injection site
   burning sensation ←- hypertonicity
   diluting the nutrients
   re-positioning the needle
   self-limited
   lasts between one and two weeks

Treatment of ADR

- Anaphylaxis
  Standard emergency procedures
- Vasovagal reactions
  Keep the IV open – slow it down
  Elevate the feet and legs
  Administer O2 at 3-6L/min

ABC's of giving an IVNT

- Monitoring for side effects
- Things that must be within reach
  Epi 1:1000
  O2, mask & cannula
  Laryngoscope with multiple sizes of E-T tube

사용하는 IV 제제

- Kyominotin 2 ample
  Glycyrrhizinate 53㎎
  Glycine 400㎎
  Cysteine 15.37㎎
- Magnesium
  Mg 2000 mg
- Beecom hexa 1 ample
  Nicotinamide 40mg
  B1 10mg
  B12 10㎍
  B2 5.47mg
  B6 5mg
  Dexpanthenol 5.17mg
- Dutenol
  Dexpanthenol 500mg
- Thiamine
  Thiamine 50mg
- Bidoxin
  Pyridoxin 50mg
- Mega-C
  Vit C 10g
- Bivon
  8 cc $NaHCO_3$
- Glutathione
- Selenium

만성피로시 IVNT

MgCl	10 cc(2.0g)
Pantothenic acid (B5)	2 cc (500mg)
Pyridoxine(B6)	1 cc (50mg)
Vitamin C	20 cc(10g)
Bivon	8 cc
B-complex	1 ample
B1	50 mg
Reduced Glutathione	*10 cc(600mg): 따로 IV*
Glycyrrhizic acid	*2 ample*
Selenium	*0.5 ample*
Amino Acid	

Vitamin C

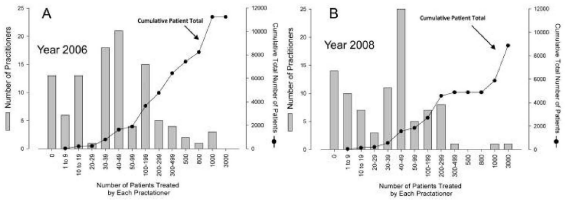
- ↓ oxidative stress upon the mitochondria
- ↓electron leakage which has been associated with fibromyalgia & CFS
- Supports adrenal gland function
- Coenzyme for the conversion of L-dopa to NE: an important part of the physiologic stress response

Vitamin C: Intravenous Use by Complementary and Alternative Medicine Practitioners and Adverse Effects

- Attendees at CAM Conferences in 2006 and 2008
- Of 199 survey respondents (out of 550), 172 practitioners
  - IV vitamin C to 11,233 patients in 2006
  - 8876 patients in 2008
- Average dose was 28 grams every 4 days, with 22 total treatments per patient.

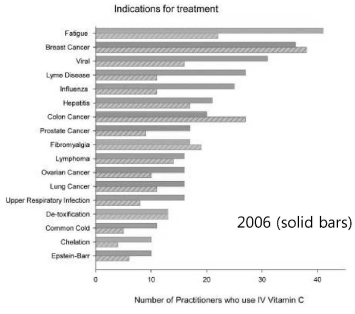
PLoS One. 2010; 5(7): e11414.

Cumulative total and the distribution of patients treated among the survey respondents



PLoS One. 2010; 5(7): e11414.

Number of practitioners who used intravenous vitamin C for various conditions



2006 (solid bars) and 2008 (hatched bars)

PLoS One. 2010; 5(7): e11414.

B-complex

- Required for ATP production in glycolysis, TCA cycle and the electron transport chain
- Folic acid deficiency
  - → subclinical or clinical macrocytic anemia & fatigue
- Riboflavin (B_2)
  - ↓ neuromuscular irritability(cramping/spasm) often accompanying CFS
  - helpful for fatigue as it is required for production of the FADH molecule and energy production
  - ↑mitochondrial function by ↑FADH production
- Vit B_5
  - required for adrenal hormone, metabolism of fatty acids, protein and CHO

Vit B_6

- Coenzyme for Mg and synergist of Mg
- Required coenzyme for hundreds of metabolic reactions
- Improve tingling, pain, weakness & numbness

Vit B12

- In Fatigue pts,
  - impaired transport of vit B_{12} across the BBB,
  - accelerated breakdown of vit B_{12} in the brain

CFIDS Chronicle 1997(Winter):57

- Recommended I.M in the morning d/t excitatory effect of vit B_{12}

CFIDS Chronicle 1999(Nov/Dec):14-16

Magnesium

- Major role in reactions involving ATP, DNA & RNA
- Many enzymes (over 400) require Mg
- Required for the shuttling of potassium intracellularly
- Often deficient in fibromyalgia – 45%
  - low at sites of tenderness in pts with fibromyalgia
- In balance with Ca - between 2:1 and 1:2
  - good to reduce intracellular Ca & abnormal calcification

Arthritis Rheum 1994;37:790-793

Magnesium

- Highly concentrated in the adrenal gland
- Required in the TCA cycle as Mg for energy production
- Sx of CFS are quite similar to Mg deficiency
  - IV Mg → rapid resolution of chronic muscle pain
- Helps regulate blood sugar balance

Magnes Trace Elem 1990;9:333

Glutathione

- Required for the proper function of the Hexosmonophosphate Pump required for Hb production
- Helps shunt Mg into cells

Glycyrrhizic acid

- component of licorice root
- reduce AST, ALT in serum
- inhibits immune-mediated cytotoxicity against hepatocytes and NF-kappa B
- powerful antiviral effects particularly against hepatitis C
- Lower estrogen, raise progesterone
- aldosterone-like effects
  - Licorice root >3g/d or glycyrrhizin acid >100mg/d, >6 weeks
  - Na and water retention, HTN, hypokalemia, renin-aldosterone inhibition
  - BP, electrolyte monitoring
  - Recommend potassium intake

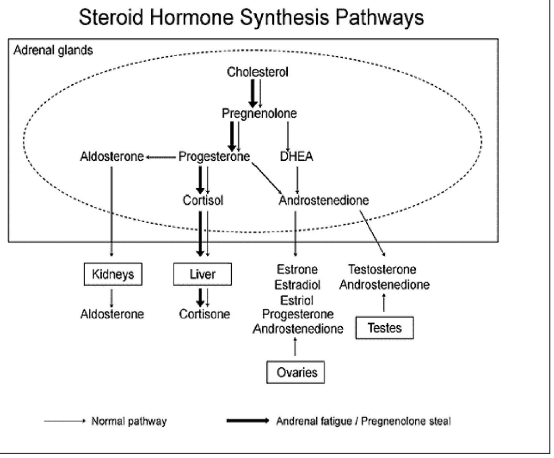
Glycyrrhizic acid

- Supports the adrenal gland
- ↑ cortisol availability

Arzneimittelforschung 1979;2994):647-649
Clin Sci(Colch)2002;102:203-211

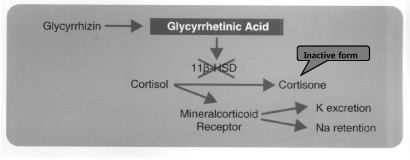
- Effects of glucocorticoids & mineralocorticoids by slowing the rate of their catabolism

Endocrinol Jpn 1990;37:331-341
Arzneimittelforschung 1979;2994):647-649
J Clin Endocrinol Metab 1956;16:338-349
Endocrinol Jpn 1957;4:17-27



Glycyrrhizic acid

- Inhibit dehydrogenation of cortisol
- Prolong the life of progesterone, exert a weak amphoteric estrogenic action and improve general gonadotropic rhythms in body



Korean Integrative Medicine Institute 14th International Symposium on Functional Medicine

Amino Acids (8.5%)

- required for detoxification, immune function
- Tyrosine
  - required for the synthesis of thyroid hormone
  - enhance dopamine, catecholamine synthesis
  - improve stress-associated declines in noradrenaline and performance
- Phenylalanine
  - Precursor to tyrosine, depamine, L-dopa, NE, epi
  - All required for a proper stress response

Amino Acids (8.5%)

- Subnormal 24-hour urinary excretion in CFS pts
  - methionine, phenylalanine, isoleucine, lysine, tryptophan, valine, leucine

J Nutr Med 1991;2:369-375

- significant clinical improvement after 3 months in 15 of 25 pts with CFS

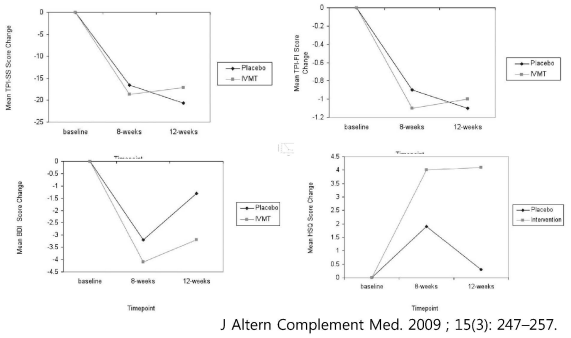
J Appl Nutr 1994;46(3):74-78

Intravenous Micronutrient Therapy (Myers' Cocktail) for Fibromyalgia: A Placebo-Controlled Pilot Study

- **Subjects;** 34 adults with ACR-defined FMS.
- **Intervention**
  - treatment (weekly infusions of IVMT) for 8 weeks
  - placebo (weekly infusions of lactated Ringer's solution)
- **Outcome measures**
  - Tender Point Index, assessed 8 and 12 weeks after initiation.
  - Visual Analog Scale to assess global pain,
  - Physical function (Fibromyalgia Impact Questionnaire), mood (Beck Depression Index), quality of life (Health Status Questionnaire 2.0).

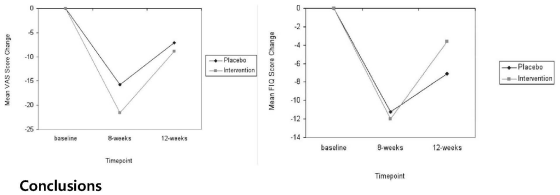
J Altern Complement Med. 2009 ; 15(3): 247–257.

Change in Outcome Measures at 8 Weeks Following Treatment



J Altern Complement Med. 2009 ; 15(3): 247–257.

Change in Outcome Measures at 8 Weeks Following Treatment



Conclusions

- Most subjects experienced relief as compared to baseline,
- but no statistically significant differences were seen between IVMT and placebo.

J Altern Complement Med. 2009 ; 15(3): 247–257.

What is Fibromyalgia (FMS)?

- Clinical syndrome of unknown etiology and pathogenesis
- Characterized by musculoskeletal pain, non restorative sleep and fatigue, psychiatric, neurological and other symptoms

From Practice, to Theory-

- Predisposing Factor HLA Susceptibility or Precipitating Factors (Trauma/Medical illness)
  - Autoimmune Disorder: Formation of autoantibodies to surface proteins on myocytes or endothelial cells
  - Deficiency in Nitric Oxide Production or Impaired Release of, or Response to, Nitric Oxide
  - Vasomotor Dysregulation
  - Muscle Hypoperfusion
  - Impaired intracellular energetics
  - Induction of Pain
- **Katz DL et al. The Pain of Fibromyalgia Syndrome is due to Muscle Hypoperfusion Induced by Regional Vasomotor Dysregulation. Medical Hypotheses: In press**

Arginine

- Precursor to NO production
- Vasodilatory influence
- Ameliorates endothelial function
- Also:
  - Promotes production of growth hormone. FM patients have an abnormal sleep pattern involving stages 3 and 4 of non REM sleep. As GH is secreted predominantly during stages 3 and 4 of non-REM sleep, it was originally hypothesized that FM patients may have impaired GH secretion

Vitamin B3, B6, tryptophan and magnesium

- FMS patients may be deficient in serotonin because the tryptophan obtained from food metabolizes into kynurenin rather than to tryptophan and 5-htp.
- 5-htp is likely to be more efficient than L-tryptophan in boosting serotonin.
- A combination of Vitamin B3 and B6 plus tryptophan and magnesium addresses serotonin deficiency.

Malic acid

- FMS is the result of local hypoxia to the muscles.
- Muscle biopsies from affected areas showed muscle tissue glycolysis is inhibited, reducing ATP synthesis.
  -→ This stimulates the process of gluconeogenesis, which results in muscle tissue breakdown and mitochondrial damage.
- Malic acid reverses hypoxia induced inhibition of glycolysis and energy production, possibly improving energy production in fibromyalgia, and reversing the negative effect of the relative hypoxia

About FMS

- The needs of FMS patients are not fully met at present
- Practice may inform theory; theory may then serve to advance practice
- If a causal pathway for FMS can be established, we can better direct our efforts at breaking the links

Magnesium for headache

- Magnesium (1 gram iv acutely)
  - (soy beans, black beans, tofu, seeds, nuts, whole grains, shellfish)

Mauskop. Headache, 2002; Pfaffenrath. Cephalgia, 1996
Mazzotta. Cephalgia, 1999; Wang, Headache, 2003
Peikert. Cephalgia, 1996; Facchinetti F, Headache, 1991

Magnesium - mechanism

- Ionized magnesium levels low in 50% of MHA patients
- Migraines associated with platelet aggregation, serotonin release
- Magnesium reduces platelet aggregation
- Magnesium decreases the affinity of serotonin for vascular receptor sites
- Magnesium acts as an NMDA receptor (glutamate receptor) antagonist
  - NMDA receptors & pain transmission
  - Inhibits one type of neuronal spreading depression in experimental models

Consequences of Reduced Mg++

- Vasoconstriction of scalp arteries
- Reduced affinity of serotonin receptors
- Lower threshold for activation of N-methyl-d-aspartate receptors
- Enhanced platelet aggregation and serotonin release

Trials with Mg++ Supplements

- An **infusion of 1.0 g of magnesium sulfate** in 40 patients with acute migraine
  - 52% responded to therapy
  - 86% of the responders had low serum ionized Mg++ levels
  - 16% of the non-responders had low serum ionized Mg++ levels.

Mauskop A. Alternative therapies in headache – Is there a role? Medical Clinics of North America 85(4): 1077-84; 2001.

Trials with Mg++ Supplements

- Four trials with oral magnesium supplementation
- Three of the four showed efficacy
- The one negative trial used a poorly absorbed magnesium salt which resulted in diarrhea

Current Use of Mg++ Supplements

- 500 mg/day K+ Mg++ aspartate
- Avoid combining with Fe, Ca, Zn
- May cause temporary diarrhea
- Magnesium gluconate – an alternate
- Menstrual migraine – months to benefit

Mann, Doug et al. "Migraine and Tension-Type Headache." Integrative Medicine. Ed. David Rackel MD. Philadelphia: Sanders, 2006 143-156.

Summary

- IVNT appears promising for treatment of Fatigue, Myalgia, Migraine sysmptoms
- Use of IVNT is effective at present, although still over the line of evidence
- Future efforts will need to move further ‘upstream’