Comparison of Essential Trace Elements in Blood of Patients Receiving Ramathibodi Standard Parenteral Nutrition with Ramatrace or a Commercial Formular

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Objective: *Commercially intravenous trace element product is very expensive compared to Ramatrace. Therefore, the present research was designed to compare the levels of zinc, copper, chromium and manganese in the blood of patients receiving Ramathibodi Standard Parenteral Nutrition (STD) containing the Ramatrace or the commercial product.*
Material and Method: *Two groups of patients receiving STD were recruited. Group 1 (19 males and 11 females) received Ramatrace and Group 2 (19 males and 11 females) received a commercial product. Blood samples on day 0, day3 and day10 were measured for zinc, copper, chromium and manganese levels by atomic absorption spectrophotometer (model 3100, Perkin Elmer).*
Results: *The present results showed that levels of zinc, copper, chromium and manganese were not significantly different between the two groups. On day 0, day 3 and day 10, the levels of zinc, copper and manganese in the blood of both groups were significantly increased ($p < 0.05$). Blood chromium levels of Group 1 were significantly increased from day 0 (0.14 ± 0.02 μg/dL) to day 3 (0.23 ± 0.02 μg/dL) but there was no significant difference between day 3 and day 10. In Group 2, the blood levels of chromium from day 0 to day 10 were significantly increased.*
Conclusion: *In patients receiving STD, Ramatrace could improve the levels of zinc, copper, chromium and manganese as well as the commercial product. This may be one way to reduce the cost of treatment.*

Keywords: *Trace elements, Zinc, Copper, Chromium, Manganese, Ramatrace*

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Complete human nutrition requires not only carbohydrates, fats, amino acids, electrolytes and vitamins but also trace elements. These elements are the ones that constitute less than 0.05% of total human body weight. There have been many studies on the composition of trace element since 1972[1-3]. In 1979, the expert committee that was convened by the Nutrition Advisory Group of the Department of Foods and Nutrition of the American Medical Association considered Zinc (Zn), Copper (Cu), Chromium (Cr) and Manganese (Mn) necessary for the patients receiving total parenteral nutrition (TPN) to prevent trace element deficiencies[4,5]. The published guidelines suggest dosages of four trace elements and recommend a single-entity formulation[6]. In Thailand, there is only one commercial trace element injection, Addamel-N (Fresenius Kabi)[7] (Table 4), but it is much more expensive than a local preparation from Chulalongkorn Hospital and Songklanakarin Hospital. This local product contains Ramatrace. Ramatrace (Table 4) is an essential trace element solution that has been modified from the guidelines by the expert committee of America Medical Association. It is a sterile solution of Zinc (1 mg/mL), Copper (0.4 mg/mL), Manganese (0.1 mg/mL) and Chromium (0.004 mg/mL) in 3-ml vial. The objectives of

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the present study were to compare the blood levels of Zn, Cu, Cr and Mn in patients receiving total parenteral nutrition containing *Ramatrace* or the commercial formula. (Addamel N, Fresenius Kabi).

Material and Method

Patients in medical and surgical departments who could not intake enough calories via gastrointestinal feeding and were consulted for TPN at least 10 days were included in the present study. Written informed consent was obtained from all patients on admission to the study. The patients were randomized into two groups based on trace element solutions. Group 1 (30 patients) received Ramathibodi Standard adult TPN (STD) (Table 1) containing *Ramatrace*, whereas those of Group 2 (30 patients) received commercial multi-trace element solution Addamel N (Fresenius Kabi). The protocol was approved by Committee on Human Rights on Researches Involving Human Subjects. The subjects who had been treated with drugs containing alcohol, diuretic agents such as spironolactone (Aldactone®), thiazides, (Dichlortide®) and triamterene (Dyazide®) were all excluded.

Table 1. General characteristics (mean ± SEM) of patients at baseline

Parameter	Group 1	Group 2
Sex: Male/Female	19/11	19/11
Age, year	53.4±18.2	53.3±17.1
Weight, kg	56.8±1.4	58.1±1.2
Height, cm	162.9±1.3	164.1±1.2
BMI, kg/m^2	21.3±0.4	21.5±0.3
Diagnoses of patients, n (%)		
Gastrointestinal disease	16 (53%)	11 (36%)
- Gastrointestinal obstruction	5	0
- Gastrointestinal perforation	3	1
- Pancreatitis ± complications	8	10
Carcinoma	12 (40%)	15 (50%)
- Gastric carcinoma	5	5
- Esophageal carcinoma	6	4
- Colonic carcinoma	0	3
- Laryngeal carcinoma	1	2
- Retroperitoneal liposarcoma	0	1
Other diseases	2 (7%)	4 (13%)
- Multiple trauma (accident)	2	3
- AbdominalAortic Aneurysm	0	1

No significant difference between 2 groups ($p > 0.05$)

Table 2. Laboratory data of the patients

Clinical lab	Group 1		Group 2	
	Before TPN	After TPN	Before TPN	After TPN
Liver function tests				
Total protein (g/L)	63.2 ± 11.3	73.9 ± 13.3	57.3 ± 14.4	68.6 ± 10.5
Albumin (g/L)	31.6 ± 5.5	32.5 ± 7.1	30.3 ± 3.7	34.8 ± 7.6
Aspartate aminotransferase (u/L)	49.9 ± 4.3	46.2 ± 6.1	30.2 ± 4.5	28.5 ± 5.1
Alanine aminotransferase (u/L)	42.9 ± 6.5	52.3 ± 4.8	43.8 ± 6.7	45.7 ± 4.8
γ-Glutamyl transferase (u/L)	40.8 ± 19.5	37.4 ± 23.4	11.8 ± 6.2	17.5 ± 6.7
Alkaline phosphatase (u/L)	162.4 ± 64.8	156.0 ± 63.8	114.9 ± 55.5	126.1 ± 54.5
Total billirubin (mg/dL)	0.7 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.7 ± 0.3
Direct billirubin (mg/dL)	0.7 ± 0.1	0.4 ± 0.4	0.4 ± 0.2	0.4 ± 0.1
Renal function tests				
Blood urea nitrogen (mg/dL)	13.2 ± 6.5	17.0 ± 12.3	14.0 ± 9.6	22.2 ± 13.7
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.5	0.7 ± 0.3
Lipid profiles				
Triglyceride (mg/dL)	105.1 ± 14.0	108.9 ± 17.2	132.9 ± 23.0	126.1 ± 13.7
Cholesterol (mg/dL)	162.0 ± 41.5	138.4 ± 43.6	133.3 ± 69.9	139.0 ± 46.0
Electrolytes				
Sodium (mmol/L)	136.6 ± 2.9	135.6 ± 6.7	136.5 ± 2.9	136.3 ± 2.7
Potassium (mmol/L)	4.2 ± 0.4	4.4 ± 0.6	3.6 ± 0.7	4.56 ± 0.54
Chloride (mmol/L)	99.5 ± 4.7	99.9 ± 3.5	99.7 ± 3.4	98.7 ± 5.1
Carbondioxide (mmol/L)	25.2 ± 4.5	25.7 ± 3.5	24.7 ± 5.7	24.8 ± 4.8
Calcium (mg/dL)	9.0 ± 0.6	9.3 ± 0.8	8.2 ± 0.9	9.0 ± 0.6
Phosphorus (mg/dL)	2.9 ± 0.4	3.1 ± 0.5	2.7 ± 0.4	3.6 ± 0.5
Glucose (mg/dL)	130.7 ± 74.2	125.1 ± 37.0	150.7 ± 44.2	158.4 ± 46.6
Uric acid (mg/dL)	2.8 ± 1.9	2.5 ± 1.3	2.4 ± 1.2	2.8 ± 2.1

Table 3. The blood levels of four trace elements of patients receiving total parenteral nutrition with two different trace element injection

		Serum Zn μg/dL (70-120[10])	Serum Cu μg/dL (70-140[10])	Whole blood Mn μg/dL (0.44-1.32[8])	Whole blood Cr μg/dL (0.1-0.5[9])
Group 1	Day 0	76.4 ± 3.3	78.1 ± 3.4	0.57 ± 0.04	0.14 ± 0.02
	Day 3	90.4 ± 3.1[a]	93.8 ± 2.4[a]	0.76 ± 0.05[a]	0.23 ± 0.02[a]
	Day 10	92.9 ± 3.9[b]	99.5 ± 2.1[b]	0.86 ± 0.04[b]	0.26 ± 0.03[a]
Group 2	Day 0	67.8 ± 2.6	80.8 ± 3.5	0.69 ± 0.05	0.11 ± 0.02
	Day 3	82.0 ± 2.5[a]	88.5 ± 4.6[a]	0.81 ± 0.04[a]	0.21 ± 0.03[a]
	Day 10	93.7 ± 2.4[b]	100.7 ± 3.4[b]	0.90 ± 0.06[b]	0.23 ± 0.02[b]

[a] = significant difference from Day 0 at $p < 0.05$
[b] = significant difference from Day 3 at $p < 0.05$

Table 4. Standard nutritional regimens for TPN patients (volume 1.0 L bottle)

Nutrient	Amount
Calories	1100 kcal
Dextrose	250 g
Amino acid	40 g
Fat	500 kcal
Sodium	50 mEq
Potassium	40 mEq
Chloride	50 mEq
Phosphate	7.5 mM
Calcium	5 mEq
Magnesium	8 mEq
Acetate	73 mM
OMVI[1]	4 mL
Trace element solution[2]	
Vitamin C	500 mg
Bco[3]	2 mL

1. OMVI 4 mL: A 3300 iu, B_1 3 mg, B_2 3.6 mg, B_6 4 mg, B_{12} 0.005 mg ,Folic acid 0.46 mg,Nicotinamide 40 mg, Biotin 0.06 mg, Pantothenic acid 15 mg, C 100 mg, D 200 iu, E 10 mg, K 2 mg
2. Ramatrace solution 1 mL: Zn 1.00 mg, Cu 0.4 mg, Mn 0.1 mg, Cr 0.004 mg
Addamel N 1mL: Zn 0.65 mg, Cu 0.128 mg, Mn 0.028 mg, Cr 0.00104 mg, Se 0.0032 mg, Mo 0.0019 mg, Fe 0.112 mg, F 0.1 mg, I 0.0125 mg
3. Bco 1 mL: B_1 100 mg, B_2 0.5 mg, B_6 1 mg, Nicotinamide 100 mg

Blood sample collection

The blood samples were drawn from each patient before starting TPN, 3 days and ten days after initiating TPN between 6 to 7 A.M. This was used for biochemical tests such as liver function test, renal function test, electrolytes, lipid profiles, blood sugar and trace element of zinc, copper, chromium and manganese levels. The first 2 mL of heparinized whole blood was used for Cr and Mn analysis[8,9], whereas the second 5 mL of clotted blood was used for Zn and Cu analysis[10]. The blood collecting tubes were acid-washed plastic tubes. The clotted blood was centrifuged for 15 minutes at 5000 rpm. The serum was then transferred to acid-washed Eppendorf tubes. The blood levels of Zn, Cu, Cr and Mn were determined by atomic absorption spectrophotometer**,** as described previously[8-10].

Statistical analysis

Results are presented as mean ± SEM (standard error mean). A statistical significant difference was considered at a p-value test less than 0.05. Difference in general characteristics between the two groups was tested using Mann-Whitney U Test. The changes in variables between times were tested for significant differences using analysis of variance with repeated measurement (paired T-test) by using SPSS for Windows version 9.0.

Results

Sixty inpatients receiving STD at Ramathibodi Hospital were included: 30 patients in Group 1 (19 males and 11 females), with an average age of 53.4 ± 18.2 years, and 30 patients (19 males and 11 females) in Group 2, with an average age of 53.3 ± 17.1 years. There were no statistically significant differences in general characteristics, primary diagnosis and the biochemical tests as shown in Table 1, 2.

As shown in Table 3 and Fig. 1, mean (± standard error) values of Zn, Cu, Cr and Mn of both groups

Table 5. Incidence of Zn, Cu, Cr and Mn deficiency before and after trace elements supplementation

	n (%)								
	D0			D3			D10		
	Total	Gr1	Gr2	Total	Gr1	Gr2	Total	Gr1	Gr2
Zinc	17	10	7	7	5	2	4	3	1
< 70 μg/dL	(28.3)	(33.3)	(23.3)	(11.7)	(16.6)	(6.7)	(6.7)	(10.0)	(3.3)
Copper	11	6	5	3	0	3	1	0	1
< 70 μg/dL	(18.3)	(20.0)	(16.7)	(5.0)		(10.0)	(1.7)		(3.3)
Chromium	19	9	10	-	-	-	-	-	-
< 0.1 μ/dL	(31.7)	(30.0)	(33.3)						
Manganese	16	10	6	-	-	-	-	-	-
< 0.44 μg/dL	(26.7)	(33.3)	(20.0)						

Table 6. Incidence of trace elements deficiency in the diseases

Trace elements deficiency	GI diseases, n (%)	Cancer, n (%)	Other diseases
1. Trace elements deficiency	8 (13.3)	7 (11.7)	
Zinc	2 (0.03)	-	-
Copper	1 (0.02)	2 (0.03)	-
Chromium	3 (0.05)	2 (0.03)	-
Manganese	2 (0.03)	3 (0.05)	1 (0.02)
2. Trace elements deficiency	10 (16.7)	7 (11.7)	
Zinc and Copper	2 (0.03)	-	
Zinc and Manganese	2 (0.03)	1 (0.02)	1 (0.02)
Zinc and Chromium	2 (0.03)	4 (0.07)	-
Copper and Manganese	2 (0.03)	-	-
Copper and Chromium	-	1 (0.02)	-
Manganese and Chromium	2 (0.03)	1 (0.02)	-
3. Trace elements deficiency	3 (0.05)	1 (0.02)	
Zinc, Copper and Chromium	2 (0.03)	-	-
Zinc, Manganese and Chromium	-	1 (0.02)	-
Copper, Manganese and Chromium	1 (0.02)	-	-
Total	21 (35.0)	15 (25.0)	

on day 0,day 3 (the third day after receiving STD) and day10 (the tenth day after receiving STD) were all progressively and significantly increased, but there was no difference between day 3 to day 10 of whole blood Cr levels in Group 1.

Furthermore, there was no difference between the two groups with regard to each blood level of the four trace elements. Table 5 shows the incidence of deficiency of trace elements before and after supplementation. The incidence in percentage of Cr, Zn, Mn and Cu deficiency was 31.7, 28.7, 26.7 and 18.3, respectively. After trace elements supplementation, the authors found Zn deficiency in Group I decreased to 16.7% and 10% at day 3 and day 10 whereas those of Group II decreased to 6.7% and 3.3%, respectively. At day 3 and day 10, Group 1 showed no Cu,Cr and Mn deficiency whereas, those of Group 2 showed Cu deficiency 10% at day 3 and decreased to 3.3% at day 10.Table 6 shows the incidences of trace element deficiency in various diseases. The patients with gastrointestinal tract diseases had trace element deficiency about 35% whereas, 25% was found in those with carcinoma.Some patients had trace element deficiency more than one (Table 6).

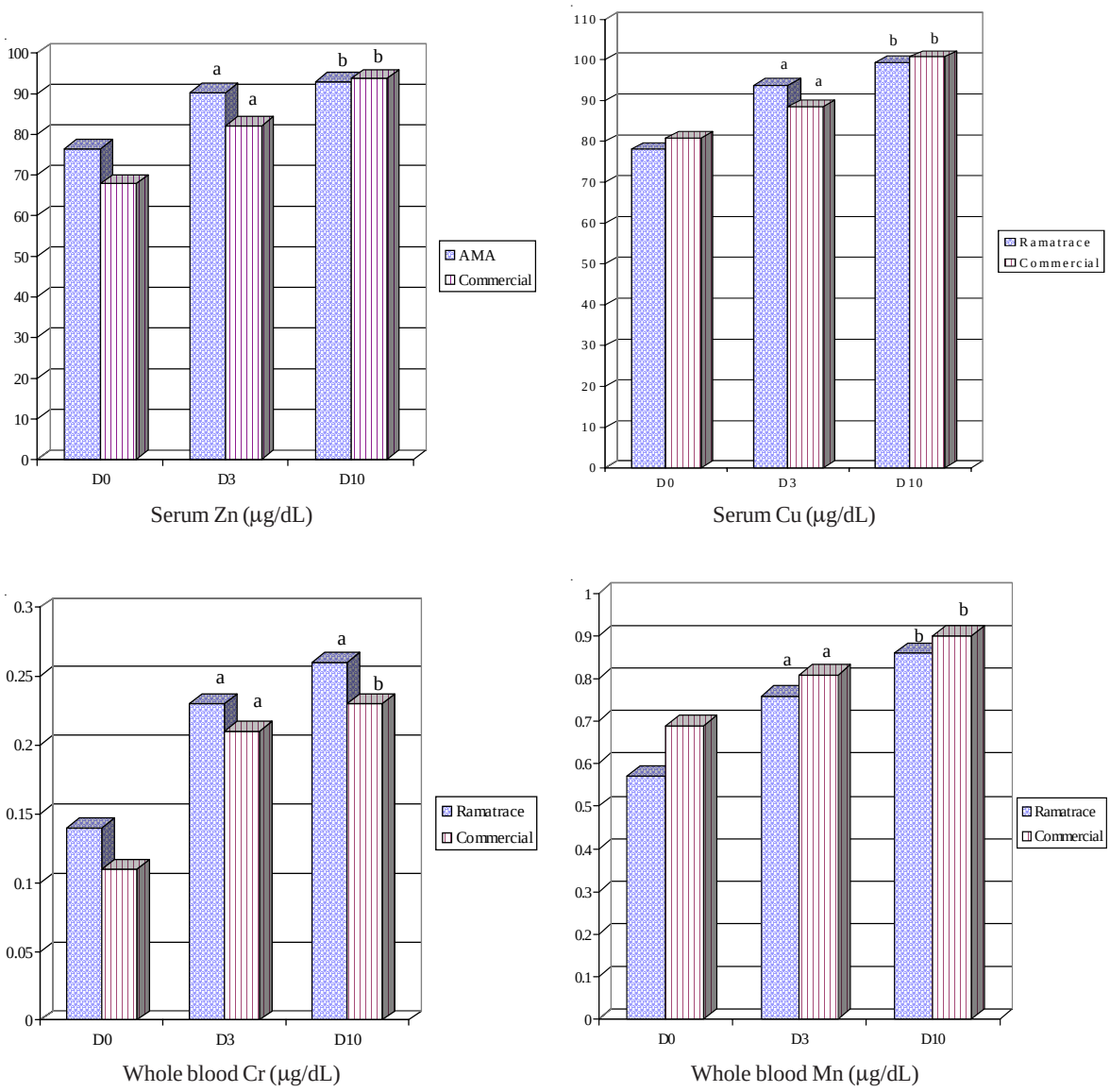

Fig. 1 Serum Zn and Cu, whole blood Cr and Mn concentrations of patients receiving *Ramatrace* and commercial trace element

Discussion

Total parenteral nutrition is an important adjunct in the care of patients who are unable to meet their nutritional needs by utilizing the digestive tract for a prolonged period of time. Hypertonic nutrient solutions could be administered via catheters in central veins[11]. The nutritional solution used contains the essential trace elements[12,13] because their deficiency leads to various pathologic states, some of which are very serious and dangerous. Zn, Cu, Cr and Mn are recommended by AMA[6]. Cu and Zn deficiencies associated with TPN were the first trace element deficiencies described[13,14].

The assessment of trace element status is extremely difficult.At present, there is no universal answer to determine whether trace element repletion

occurs early or later in the course of TPN. In the present study, blood levels of Zn, Cu, Cr and Mn were determined by atomic absorption spectrophotometer. Zn and Cu were determined from serum while Cr and Mn were determined from whole blood. The diagnosis of sixty patients is shown in Table 1. Sixty inpatients receiving STD were included: 30 patients in each group with 19 males and 11 females, average age of 53.4 $\pm$ 18.2 years and 53.3 $\pm$ 17.1 years in Group 1 and Group 2, respectively. Primary diagnoses were reasonable equally distributed and are shown in Table 1.

The blood levels of Zn, Cu and Mn were within the normal range in Group 1 and Group 2.The levels increased after receiving STD with both the *Ramatrace* and commercial formula (Table 3). The blood levels of Cr were higher than the upper limit of the normal range (0.1-0.5 μg/dL). The acute LD_{50} values of intravenous trivalent chromium in rats were reported as high as 10 to 18 mg/kg (15). No specific manifestations of chromium toxicity are anticipated from parenteral administration[15].

The blood levels of Zn, Cu and Mn of both groups after receiving STD with trace elements increased significantly (Fig. 1) ($p < 0.05$). The blood levels of Cr in Group 1 on day 3 and day10 were not significantly different, whereas those in Group 2 were significantly increased (Table 3).

The immediate supplementation from day one of therapy may be in the best interest of the patient since the patient may be depleted long before institutional admission[15]. As shown in Tables 5 and 6, the incidence of each trace element deficiency ranged about 18.3-31.7%, and after 10 days of both trace element supplementations, Zn deficiency was found in both groups at about 3.3-7.8% and most of them were diagnosed with GI diseases such as pancreatitis and duodenal perforation. Moreover, the duration of supplement to correct serum Zn deficiency may need longer than 10 days. In North America and New Zealand, overt and severe nutritional Zn deficiency was first recognized in patients receiving either parenteral nutrition or enteral feedings without zinc supplements[16,17]. Secondary Zn deficiency was also documented in the presence of certain disease states such as cystic fibrosis, as well as in renal and liver disease, and in association with burns and alcoholism[17]. Zn deficiency may arise from increased excretion of zinc in urine (hyperzincuria) and/or loss of zinc via intestinal secretions and exudates[18].

After 3 days of supplement with *Ramatrace*, no Cu deficiency was found, whereas with the commercial solution,Cu deficiency was observed and most of the patients had gastrointestinal diseases. Cu deficiency has been observed in some patients receiving home TPN and it appears as a microcytic anemia, which may be mistaken for pyridoxine deficiency[19].

Cr deficiency has been reported in patients on long-term TPN[20], and it manifests itself as a sudden diabetic state in which blood sugar is difficult to control, along with neuropathy and encephalopathy. Most cases occur in persons with special problems such as total parenteral nutrition diabetes or malnutrition. Cr deficiency is characterized by glucose intolerance, glucosuria, hypercholesterolemia, decreased longevity, decreased sperm counts, and impaired fertility[5]. Morradian and Morly[21] reported that diabetic patients usually have low serum Cr and Zn levels. There were four diabetic patients and one hypercholesterolemic patient who had low whole blood chromium levels (Table 6).

So far, there are no reported cases of total parenteral nutrition-induced Mn deficiency. Mn deficiency has been associated with cancer, rheumatic conditions, rickets, morning sickness, jaundice, and diabetes. In the present study, as shown in Table 6, there were four patients who had cancer and two patients who were diabetic. Other diseases have not been reported. Takagi Y et al[22] mentioned that Mn could cause serious liver dysfunction [aspartate aminotransferase > 100 u/L, alanine aminotransferase > 100 u/L, and total bilirubin > 3.4 μmol/L (2 mg/dL)]. It was found in the present study that there were no patients with aspartate aminotransferase > 100 u/L, two patients with alanine aminotransferase > 100 u/L and five patients with total bilirubin > 2 mg/dL.

Low serum Mn concentrations, usually association with low concentrations of Cu and Zn, have been found in persons with impaired bone metabolism[23]. In the present study, there was one diabetic patient who had low blood Zn, Cr and Mn concentrations.

The present study showed that multi-trace elements were available for patients, both AMA modified formula and commercial formula. Although commercial trace element formulas have more elements than AMA modified formulas, four trace elements are enough for the patients. The preparation of AMA modified multi-trace element solutions must be produced and assayed according to USP standard. The raw materials should be trace element free water,and purified chemicals. Be careful to prevent contamina-

tion of external trace elements from equipment and process. The finished products must be assayed and verified safe for the patients. They were comfortable with use in a once daily package.

Conclusion

The present study showed both *Ramatrace* and commercial formula could increase blood levels of Zn, Cu, Cr and Mn. There was no significant difference in blood levels of the four trace elements. They are used both to prevent depletion and to maintain the patients' nutritional status. So, the *Ramatrace* could be used instead of a commercial one, since the commercial trace element is more expensive (240 baht/ampoule/day) than Ramatrace (34 baht/vial/day).

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การเปรียบเทียบแร่ธาตุสำคัญที่ร่างกายต้องการใช้ปริมาณน้อยในเลือดของผู้ป่วยที่ได้รับสารอาหารทางหลอดเลือดดำซึ่งผสมยาฉีด รามาเทรซ กับยาฉีดที่ผลิตโดยบริษัทยาต่างประเทศ

จุฬาภรณ์ รุ่งพิสุทธิพงษ์, จิราภรณ์ เชี่ยววิทย์, ศรีวัฒนา ทรงจิตสมบูรณ์, บุษบา จินดาวิจักษณ์

วัตถุประสงค์: *ยาฉีดของแร่ธาตุสำคัญที่ร่างกายต้องการปริมาณน้อยที่ผลิตโดยบริษัทยาต่างประเทศมีราคาแพงเมื่อเปรียบเทียบกับรามาเทรซ ดังนั้น จึงต้องการศึกษาระดับของสังกะสี ทองแดง โครเมียมและแมงกานีสในเลือดของผู้ป่วยที่ได้รับสารอาหารทางหลอดเลือดดำซึ่งผสมยาฉีดแร่ธาตุที่ผลิตขึ้นเอง (รามาเทรซ) ซึ่งมีแร่ธาตุทั้งสี่ชนิดตามที่สมาคมแพทย์แห่งสหรัฐอเมริกากำหนดไว้ กับยาฉีดของแร่ธาตุที่ต้องการปริมาณน้อยที่ผลิตโดยบริษัทยาต่างประเทศเพื่อช่วยในการตัดสินใจใช้ทดแทนกัน*

วัสดุและวิธีการ: *ผู้ป่วยที่ได้รับสารอาหารทางหลอดเลือดดำของโรงพยาบาลรามาธิบดีจำนวน 60 คน แบ่งเป็น 2 กลุ่ม กลุ่มละ 30 คน มีผู้ชายกลุ่มละ 19 คน และผู้หญิงกลุ่มละ 11 คน กลุ่มที่ 1 ได้รับ รามาเทรซ ส่วนในกลุ่มที่ 2 ได้รับแร่ธาตุของบริษัทยาจากต่างประเทศ ทำการเจาะเลือดผู้ป่วยเพื่อตรวจหาปริมาณแร่ธาตุทั้งสี่ชนิดก่อนได้รับสารอาหารทางหลอดเลือดดำ และหลังจากได้รับแล้วในวันที่ 3 และวันที่ 10 ตามลำดับ การวิเคราะห์แร่ธาตุในเลือดใช้วิธีอะตอมมิคแอบซอร์บชัน สเปรคโตรโฟโตเมตริก*

ผลการศึกษา: *พบว่าแร่ธาตุของสังกะสี ทองแดง โครเมียมและแมงกานีสทั้งสี่ในเลือดของผู้ป่วยเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติทั้ง 2 กลุ่ม และให้ผลไม่แตกต่างกัน ยกเว้น ธาตุโครเมียมในกลุ่มที่ 1 มีระดับก่อนได้รับยาฉีดแร่ธาตุ (0.14 $\pm$ 0.02 μg/dL) และเพิ่มขึ้นในวันที่ 3 (0.23 $\pm$ 0.02 μg/dL) แต่ไม่เพิ่มขึ้นในวันที่ 10 ซึ่งต่างจากกลุ่มที่ 2 ที่ได้รับยาฉีดแร่ธาตุของบริษัทยาจากต่างประเทศ ซึ่งเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ*

สรุป: *สามารถใช้ยาฉีดแร่ธาตุ รามาเทรซ เพื่อทดแทนการใช้ยาฉีดแร่ธาตุที่นำเข้าจากบริษัทยาต่างประเทศได้เป็นหนทางหนึ่งในการลดค่าใช้จ่ายในการรักษาผู้ป่วยด้วยสารอาหารทางหลอดเลือดดำ*