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Original Article

Paediatrics Section

Comparison of Various Infant Milk Substitutes with the Guidelines by European Society of Paediatric Gastroenterology, Hepatology and Nutrition: A Cross-sectional Study

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ABSTRACT

Introduction: When mother's milk is not available, Infant Milk Substitutes (IMS) must be supplemented with medical advice. Human milk can be digested easily because of the whey protein present in it and which is less in other animal milk. Considering this fact the manufacturers have attempted to make IMS as close to breast milk.

Aim: To compare the composition of different IMS with breast milk, and with international guidelines given by European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

Materials and Methods: A cross-sectional study was performed between April to May 2020, at a tertiary centre in Puducherry, India. Total 11 whey protein containing IMS brands that were commercially available in the Indian market for children aged up to six months were included in the study. The IMS for preterm babies and those without whey protein like hydrolysed milk, IMS with soya bean extract were excluded from the study. The details of IMS was collected and compared. The composition of the IMS was taken from the information provided by the manufacturer. The data was entered in Microsoft excel and was analysed using statistical software Statistical Package for the Social Sciences (SPSS) version 20.0.

Results: With respect to calories, protein, fats and vitamins all IMS met the requirements. Nucleotide content exceeded in 18.1%. Sialic acid was added in 9% IMS. Iron content is more than the ESPGHAN requirement in 9% IMS.

Conclusion: All the IMS were almost within the range advised by ESPGHAN. The children who fail to gain adequate weight can be given the brands with more calories. Babies with features of iron deficiency, can be given Brand VIII. For parents who cannot afford to buy the IMS with smart nutrients, they can choose the basic IMS which are of low cost, but meets the requirements.

Keywords: Breast milk, Lactose, Supplements, Whey protein

INTRODUCTION

Mother's milk is the best source of nutrition for all infants. It is better to practice the optimal breast-feeding steps given by Baby Friendly Hospital Initiative (BFHI) [1]. Breast feeding is an excellent way of providing ideal food for healthy growth and development of the baby. It also meets psychological and physiological needs of the infant. The IMS existed much before the era of formula milks. Even during the times, children who could not be given their mother's milk were fed by surrogate mothers. If that was not possible, they used the milk of other mammals. Surrogate mothers were popular during the early stages of nineteenth century. Later they started using milk from other mammals when the knowledge and technology improved. In 1867, Liebig's food for infants was introduced. Adaption to synthetic milk happened in 1915 which is the basis for all the commercially available IMS [2].

In exceptional circumstances where human breast milk cannot be given, IMS can be used. There are various IMS available in the market each with different constituents, that satisfies the nutritional requirement of a baby during first six months of life. The World Health Organisation (WHO) defines IMS as any food or beverage that substitutes breast milk partially or totally [3]. The IMS must be supplemented with medical advice for infants for their optimal growth and development [4,5].

The ESPGHAN is a multiprofessional organisation that aims at promoting health needs related to gastrointestinal tract and nutrition. They have specific guidelines addressed in commission directive 91/321/EEC [6]. The expected minimum and maximum requirements of different components in IMS has been mentioned in the directive.

There is a scarcity of literature comparing different IMS. There is also a need to spread the awareness among paediatricians about the best IMS available in the market to prescribe when indicated. The IMS manufacturing companies have attempted to make IMS as close to breast milk as possible. But there are variations among the IMS in composition and the cost. There is a need to study the composition of these formulations to know if it is comparable with human milk, and to find out the best option of IMS for different indications. Considering this fact, the present study aimed to compare the composition of 11 IMS with breast milk, and with the ESPGHAN guidelines.

MATERIALS AND METHODS

A cross-sectional study was performed between April to May 2020, at a tertiary centre in Puducherry, India after obtaining permission from the review board and Institutional Ethics Committee (IEC: RC/19/54).

Inclusion criteria: The various term whey protein containing IMS brands that are commercially available in the Indian market for children aged up to six months of age were included in the study.

Exclusion criteria: The IMS for preterm babies and those without whey protein like hydrolysed milk, IMS with soya bean extract were excluded from the study.

Total 11 IMS products were included in the study. All the details of the various term whey protein containing IMS products for children aged up to six months was collected and compared with reference range of breast milk and with the ESPGHAN guidelines [6-14].

STATISTICAL ANALYSIS

The data was entered in Microsoft excel and was analysed using statistical software SPSS version 20. Descriptive statistics, like frequency and percentage, was calculated for qualitative variables. All the available brands were coded to avoid bias and maintain anonymity.

RESULTS

All the 11 IMS products were compared with the standards given by the ESPGHAN, but when comparing with breast milk, there were minimal differences. The details on comparison are summarised in [Table/Fig-1]. The composition of IMS brands is summarised in [Table/Fig-2].

Composition	ESPGHAN criteria	Breast milk	Constituents in brands I-XI (Range)
Energy (kcal)	60-70	67	66.08-68.2
Carbohydrate (g/100 kcal)	9-14	10.4	9.85-12.15
Sialic acid (mg/100 mL)	N/A	30-150 mg/ 100 mL	25#
Lactose (g/100 kcal)	≥4.5	10.4	4.8-12.5
Maltodextrin (g)	N/A	-	4.5*
Protein (g/100 kcal)	1.8-3	1.8	2.1-2.8
Whey/casein	N/A	60/40	60-70/30-40**
Nucleotides (mg/100 kcal)	≤5	9.7±4.1	2.2-10.74
LIPIDS			
Total fat (g/100 kcal)	4.4-7	5.6	4.4-5.5
Milk fat (g/100 mL)	N/A	N/A	0-2.3 g
SFA (g/100 mL)	20% of total fat content	35-40%	0-1.64$$$
MUFA (g/100 mL)	≤1% total fat	45-50%	0.55-1.52
Oleic acid (g/100 mL)	N/A	35.5%	1.09-1.39##
PUFA (g/100 mL)	N/A	15%	0.5-0.83
Trans FA (g/100 mL)	3% total fat	1% of total fat	0-0.112***
Cholesterol (g/100 mL)	N/A	3.36-12.98 mg	2.6-6.84
Alpha linolenic acid (mg/100 kcal)	≤500 mg/ 100 kcal	13.4	61-110
Linoleic acid (mg/100 kcal)	300-1200 mg/ 100 kcal	510	602.9-835.8
Arachidonic acid (mg/100 mL)	1% total fat	0.45	7.4-23###
Docosahexaenoic acid (mg/100 mL)	≤Content of AA	0.3	7.4-12.8$
VITAMINS			
Thiamine (mcg/100 kcal)	60-300	23.8	70.1-104.8
Riboflavin (mcg/100 kcal)	80-400	64.1	138.9-168
Niacin (mg/100 kcal)	0.3-1.5	0.25	0.65-1.32
Pantothenic acid (mg/100 kcal)	0.4-1.2	0.37	0.4-0.83
Vitamin B6 (mcg/100 kcal)	35-175	16.4	55.5-98.5
Vitamin B12 (mcg/100 kcal)	0.1-0.5	0.03	0.13-0.39
Folic acid(mcg/100 kcal)	10-50	26.8	14.4-22.2
Biotin (mcg100 kcal)	1.5-7.5	2.98	2.5-5.16
Vitamin K (mcg/100 kcal)	4-25	22.4	6.5-11.6
Vitamin A (mcg RE/100 kcal)	60-180	79.1	79.3-115.6
Beta carotene (mcg/100 kcal)	N/A	34.3	27$$
Vitamin E (mg TE/100 kcal)	0.5-5 mg	0.2	0.68-2.1
Vitamin D (mcg/100 kcal)	1-2.5	0.02-0.37	1.07-2
Vitamin C (mg/100 kcal)	10-30	6.4	10.2-23.75
MINERALS			
Sodium (mg/100 kcal)	20-40	23.9	24.3-36.5
Potassium (mg/100 kcal)	60-160	82	80.3-125
Chloride (mg/100 kcal)	50-160	64.1	51.3-65.5
Copper (mcg/100 kcal)	35-100	59.7	38.1-79.4
Manganese (mg/100 kcal)	1-100	Trace	4.9-20.08
Selenium mcg/100 kcal	1-9	2.24-2.69	2.33-5.54
Zinc (mg/100 kcal)	0.5-1.5	79.1	0.32-0.79
Iron (mg/100 kcal)	0.3-1.3	0.07-0.22	1.02-1.88
Iodine (mcg/100 kcal)	10-50	10.44	11.44-17.62
Calcium (mg/100 kcal)	50-140	49.2	54.9-98.9
Phosphorus (mg)	25-90	22.4	29.4-59.4
Magnesium (mg/100 kcal)	5-15	5.97	5.97-11.8
Taurine (mg/100 kcal)	≤12	7.46	6.02-8.5
Choline (mg/100 kcal	7-50	1.94	7.9-25.6
Carnitine (mg/100 kcal)	≥1.2	1.2-1.56	1.2-2.2

[Table/Fig-1]: Comparison of IMS with breast milk and ESPGHAN guidelines.
All compositions were compared using the same standardised units; *Data on maltodextrin is available only for one brand (brand III); **Data on whey/casein is not available for four brands (III,IV,V,VIII); ***Data on oleic acid is available only for three brands (I,IX,XI); #Data on Sialic acid is available only for one brand (brand VIII); ##Two brands have not mentioned about trans fat (III,VIII); ###.$Only four brands have mentioned the data on AA and DHA (IV,VI,VIII,IX); $$Data on beta carotene is available only for two brands (brand IX and XI); $$$Data on saturated fat of brand VIII is not available

The energy, protein, total fat and carbohydrates were within the recommendations of ESPGHAN. The protein content in breast milk is less comparatively than in IMS. The nucleotides in brand IV and V were more than the expected range and four brands did not quantify nucleotides. Total fat content in breast milk is more than in IMS, though not significant. Ten IMS had higher saturated fatty acid content, while there was no mention in brand VIII. Only four IMS brands had AA and DHA (Brand IV, VI, VIII, IX). Only brand VIII had sialic acid. Only three brands-brand I, IX, XI-had oleic acid.

An 11 (100%) IMS meet the requirements of vitamins and minerals as per ESPGHAN, except iron. Iron content exceeded normal limits in 7 (63.6%) brands. Calcium Phosphorus ratio was between 1-2, as per ESPGHAN criteria; 2 (18.1%) IMS had the ratio equal to two (brand VII and XI); 9 (87.9%) of IMS had the ratio between 1 and 2. But the vitamin and mineral components are more than the breast milk, though not significant.

DISCUSSION

When the scientific knowledge improved, various manufacturers added multiple micronutrients to IMS to simulate breast milk, thus increasing the risk for potential adverse interactions. Ideally, infant formulae should contain only the substances to satisfy the requirements of minerals, vitamins, amino acids, other nitrogen compounds and other substances having a specific nutritive purpose [10].

Per 100 mL	Brand I	Brand II	Brand III	Brand IV	Brand V	Brand VI	Brand VII	Brand VIII	Brand IX	Brand X	Brand XI
Energy kcal	68	68	67	67	67	67	67	68	68.2	66.08	67.2
Carbohydrates											
Carbohydrate (g)	7.63	7.76	7.12	6.6	6.6	8.03	8.16	7.1	7.97	7.714	8.17
Sialic acid (mg)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	25	N/A	N/A	N/A
Lactose (g)	7.63	3.27	N/A	N/A	N/A	8.03	N/A	N/A	7.97	8.274	8.17
Maltodextrin (g)	N/A	4.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Proteins											
Protein(g)	1.49	1.49	1.48	1.91	1.91	1.46	1.47	1.43	1.49	1.56	1.49
Whey/casein	60/40	60/40	N/A	N/A	N/A	70/30	65/35	N/A	60/40	N/A	60/40
Nucleotides (mg)	1.69	N/A	N/A	7.2	7.2	1.48	N/A	2.6	3.38	2.1	1.69
Lipids											
Total fat (g)	3.51	3.44	3.63	3.7	3.7	3.23	3.16	3.7	3.38	2.96	3.17
Milk fat (g)	1.69	1.66	1.5	1.6	1.6	N/A	1.65	1.66	2.03	1.33	1.76
SFA (g)	1.35	1.32	1.64	1.6	1.62	1.43	1.47	N/A	1.51	1.14	1.34
MUFA (g)	1.47	1.52	1.16	1.12	1.12	0.63	0.55	1.02	1.19	0.63	1.15
PUFA (g)	0.55	0.5	0.83	0.81	0.71	0.61	0.62	0.54	0.6	0.644	0.59
Trans FA (g)	0.07	0.06	N/A	0.1	0.08	0.109	0.11	N/A	0.08	0.112	0.07
Cholesterol (g)	4.73	4.73	4.2	4	6.84	2.7	3.4	5.4	5.8	2.66	4.86
Alpha linolenic acid (mg)	45.9	43.2	48	49	49	40.88	48.2	75	64.8	51.8	66.2
Linoleic acid (mg)	459	432	480	491	491	530	560	410	486	546	499.5
Oleic acid (g)	1.39	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.09	N/A	1.06
Arachidonic acid (mg)	N/A	N/A	N/A	7.4	N/A	9.1	N/A	23	12.8	N/A	N/A
Docosahexaenoic acid (mg)	N/A	N/A	N/A	7.4	N/A	9.1	N/A	11.6	12.8	N/A	N/A
Vitamins											
Thiamine (mcg)	71.01	60.75	60	60	60	48	47	63	71.5	56	71.5
Riboflavin (mcg)	102.6	94.5	100	100	100	102	96	16	114.7	96.6	114.7
Niacin (mcg)	0.66	0.66	0.45	0.46	0.46	0.436	0.44	0.92	0.81	0.44	0.81
Pantothenic acid (mcg)	0.32	0.36	0.25	0.26	0.26	0.286	0.289	0.5	0.51	0.35	0.34
Vitamin B6 (mcg)	51.3	37.8	40	40	40	52	52	67	60.7	42	60.7
Vitamin B12 (mcg)	0.2	0.15	0.15	0.17	0.17	0.15	0.09	0.27	0.27	0.119	0.27
Folic acid (mcg)	10.67	12.15	13	13	13	12.26	9.63	12.2	15.2	11.9	10.8
Biotin (mcg)	3.51	3.51	2.4	2.4	2.4	1.7	1.72	2.2	2.43	1.75	2.43
Vitamin K (mcg)	5.67	5.13	4.4	4.5	4.5	6.13	6.191	5.1	5.4	7.7	6.75
Vitamin A (mcg RE)	73.04	70.74	55	56	56	53.142	53.655	61	78.9	61.6	63.1
Beta carotene (mcg)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	27	N/A	27
Vitamin E (mg TE)	1.47	0.91	1.1	1.1	1.1	0.54	0.458	1.22	1.5	0.483	1.35
Vitamin D (mcg)	1.07	0.95	0.77	0.8	0.8	0.88	0.722	1.36	1.13	0.721	1.35
Vitamin C (mg)	8.1	8.78	9	13	13	6.94	6.879	27	16.2	6.3	8.1
Minerals											
Sodium (mg)	24.3	24.8	18	18	18	16.3	23.3	17.7	22.9	19.6	21.6
Potassium (mg)	65.48	72.09	64	66	66	68.1	64.66	74	55.3	82.6	54
Chloride (mg)	44.55	37.9	37	38	38	34.74	34.39	50	39.1	36.4	41.1
Copper (mcg)	54	45.9	51	53	53	38	38	42	48.6	25.2	47.2
Manganese (mg)	7.56	3.38	7	7	7	8.1	7.29	7.5	7.56	7.7	13.5
Selenium (mcg)	3.65	3.65	1.9	1.9	1.9	1.97	1.92	1.9	3.78	1.54	2.43
Zinc (mg)	0.54	0.47	0.39	0.49	0.49	0.43	0.34	0.48	0.51	0.21	0.46
Iron (mg)	1.28	1.08	0.98	1	1	0.81	0.688	1.22	0.81	1.05	0.81
Iodine (mcg)	10.26	10.13	9.6	10	10	10.22	10.18	10.9	12.02	7.56	9.45
Calcium (mg)	55.35	54.68	47	49	49	36.79	41.2	52	67.5	44.24	67.5
Phosphorus (mg)	35.78	40.5	30	30	30	19.75	20.63	29	40.5	26.18	33.75
Magnesium (mg)	4.73	4.73	4.1	4	4	6.13	4.12	5.4	8.1	4.48	8.1
Taurine (mg)	5.54	5.4	4.5	4.6	4.6	4.63	4.4	4.1	5.8	4.76	5.27
Choline (mg)	11.34	5.4	6.4	13	13	6.813	6.74	16.3	17.5	6.86	10.8
Carnitine (mg)	1.1	1.49	0.8	1	1	0.818	0.81	N/A	1.49	0.85	1.38

[Table/Fig-2]: Composition of different IMS available in Indian market.
N/A: Not available

As per the official journal of European Union, the minimum and maximum energy reconstituted in an IMS is 60 and 70 kcal/100 mL [10]. The IMS products with higher caloric value can be provided for malnourished children.

Earlier the protein content in the IMS was high, which was the same as cow's milk and it made the IMS inferior to breast milk [5]. But 1935 onwards there were experiments on reducing the content of protein, so that the solute load can be tolerated by the immature renal tubules of the infant. In the year 2000, the concept of whey protein-based formula was introduced [6]. Whey protein containing food has properties like solubility, gelling, foaming and emulsifying. It also has factors that boosts up immune response [15,16]. Now-a-days, IMS derived from cow's milk protein must have a protein of 1.8-2 g/100 kcal ideally and must contain amino acids that are at least equal to breast milk [6]. Different amino acids can be adequately added for improving the nutritional value of the proteins [6]. The nucleotides that can be added are cytidine, uridine, adenosine, guanosine and inosine 5 monophosphate. Nucleotides can act as growth factors and have immune modulating effect [17]. In this study, three IMS (brand I,VI,XI) did not have adequate amount of nucleotide content and two (brand IV and V) had excess nucleotides content. The presence of nucleotides increases the immune response to different vaccines like haemophilus influenza type B, oral polio vaccine and diphtheria [9]. But the same effect was noticed in babies who were on IMS, as reported by Thorell L et al., [9].

The carbohydrate content should be between 9-14 g/100 kcal. All IMS in the study met the requisite amount of carbohydrate. Lactose, maltose, sucrose, glucose, glucose syrups, precooked starch, gelatinised starch and maltodextrins are the only carbohydrates that can be used in IMS. Minimum lactose content should be 4.5 gm/100 kcal as per the guidelines [6]. All 11 (100%) met the guidelines. Only 1 (9%) IMS brand II had maltodextrin (4.5 gm/100 mL). Other brands did not mention about any other carbohydrates. Sialic acid was present only in brand VIII. It is an essential component of mucins, glycoproteins, and gangliosides, and hence important for the formation of cell membrane, membrane receptors and normal functioning of brain [18,19]. Hence, it is advisable to add sialic acid in IMS. A study done by Heine W et al., has shown that formula fed babies obtain only 20% or less amount of sialic acid than breast fed babies [18], Wang B et al., also concluded that sialic acid is abundant in breast milk and hence recommended especially for preterm babies [19].

Total fat is comparatively more in breast milk than in IMS but not significant. It is the largest source of energy. The lipid content in breast milk varies with stage of lactation, maternal food habits and also has diurnal variation [11]. Cholesterol in adequate amounts help in myelination of cells in developing brain. It is also a precursor of bile acids, sex hormones and vitamin D [20,21]. An intake of similar quantity to breast milk is recommended. But being in higher quantities than breast milk, may be harmful for the infant. Use of sesame seed oil and cotton seed oil are prohibited. Lauric acid and myristic acid (saturated fatty acids) can be used separately or as a whole. It should constitute only 20% of the total fat content in IMS [6]. Quantity of saturated fat in brand VIII could have been mentioned. According to the study done by Sánchez-Hernández S et al., the saturated fat content in IMS is more in IMS than in breast milk which is similar to present study [20]. Oleic acid is the predominant Monounsaturated Fatty Acid (MUFA) in breast milk. The content is more in IMS as per Sánchez-Hernández S et al., [20].

The two relevant Polyunsaturated Fatty Acid (PUFA) are AA and DHA. Arachidonic acid is the common n-6 PUFA and n-3 PUFA is docosahexaenoic acid. Only four IMS brands had AA and DHA (brand IV,VI,VIII,IX). The DHA content did not exceed AA content, as per the ESPGHAN guidelines. Long chain PUFA is added to the IMS to improve visual and cognitive development [22]. But it can be produced by a foetus after 33 weeks of life, so babies born after that period might not require the addition of long chain PUFA [2]. This might have been the reason for non addition by the other manufacturers. The study by Sánchez-Hernández S et al., showed that breast milk has higher content of AA and DHA than the four brands of IMS where it is added, which is contradictory to the present study [20]. But the comparison of Linoleic acid and alpha linolenic acid is similar to this study. Linoleic acid content is similar to breast milk and alpha linoleic acid content is more in IMS [20].

All brands met the vitamin and mineral requirements as per ESPGHAN guidelines, but are more than that in breast milk, except iron. The iron content in seven brands of IMS exceeded the upper limit of normal range as per ESPGHAN guidelines. The manufacturers would have added higher iron content to compensate the increasing prevalence of nutritional anaemia. The amount of taurine should not be greater than 12 mg/100 kcal, which was met by all the IMS brands in this study. Taurine is an antioxidant, and thus reduces the chance of retinal lesion and visual deterioration. It also helps in cognitive development [23]. Inclusion of taurine in IMS can be beneficial, but not a necessity.

Choline is important for the brain and to develop intelligence. It reduces Low Density Lipoprotein (LDL) level and helps to prevent liver related diseases [24]. All the IMS brands studied has the required quantity of choline 50 mg/100 kcal. L carnitine content in IMS should be a least 12 mg/100 kcal. Carnitine is essential for long chain fatty acid oxidation, catabolism of branched chain amino acid, oxidation of medium chain fatty acid, prevention of accumulation of toxic concentrations of Acyl CoA, regeneration of free coenzyme A, prevention of hyperammonaemia etc., [25]. All the IMS has the required quantity of L-carnitine. When comparing the expenses, breast milk is available free of cost, but price of the studied IMS brands ranges from Rs 310-715/-. Least for brand II and highest for brand VIII. The IMS without super nutrients have higher cost than the ones with basic ingredients. Depending on the socio-economic status, Paediatricians can advise IMS to ensure compliance.

Limitation(s)

The composition of the IMS was taken from the information provided by the manufacturer and not the actual measurement of the quantities of the various contents.

CONCLUSION(S)

The energy, protein, total fat and carbohydrates were within the recommendations of ESPGHAN. All 11 (100%) IMS meet the requirements of vitamins and minerals as per ESPGHAN, except Iron. But when comparing with breast milk, there were minimal non significant differences. The nucleotides in brand IV and V were more than the expected range and four brands did not quantify nucleotides. Ten IMS had higher saturated fatty acid content, while there was no mention in brand VIII. Manufacturers can provide all the basic details of the product in the composition table itself so that the comparison and the decision can be made on for selected indications without a dilemma.

There is a need to study the composition of IMS using quantitative test for each component and to study the purity of the components.

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