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Review

Complementary Feeding Recommendations for A Healthy Future Generation

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ABSTRACT

World Health Organization data remark that 144 million children under the age of 5 are stunted by age. In Turkish society, the high weakness and stunting rates, especially among children aged 6-8 months, are an indication that complementary nutrition practices are not given enough importance in our country. Therefore, this review, it is aimed to emphasize the importance of complementary feeding in terms of the risk of malnutrition among children and to give an example of current complementary feeding practices. It is stated that at the beginning of the 5th month, infants neuromuscular development, digestive system, and renal solute load are suitable for complementary feeding. In addition to breast milk, complementary foods should include cereals, roots and tubers, legumes, nuts and seeds, dairy, meats, eggs, vegetables and fruits rich in vitamin A. Foods with allergy risk, such as eggs and peanuts should be tried for infants between 4 and 6 months. Along with breast milk, it is stated that 6-8-month olds are fed 2 or 3 times a day, and 9-11-months-old fed 3 or 4 times a day and should be paid attention to hunger and satiety signals. Complementary feeding should be started at 2 or 3 teaspoons and be increased considerably and transition should be made from pureed foods lumpy foods, finger foods and then chopped family foods until they are 12 months old. During the first year, vitamin D and iron micronutrient supplementation should be followed. It is recommended for infants to sip water instead of sugary drinks like fruit juices at meals and to introduce gluten to infants between 4 and 12 months. It is warned not to add sugar, salt and honey to the complementary feeding. To reduce the risk of malnutrition among children in Türkiye, complementary feeding should be given due significance.

Keywords: Complementary feeding, malnutrition, infant

INTRODUCTION

The World Health Organization (WHO) defines "Complementary feeding is as the process starting when breast milk alone is no longer sufficient to meet the nutritional requirements of infants, and therefore other foods and liquids are needed, along with breast milk."[1] Starting complementary feeding around the age of 6 months, as the months the infant is developmentally ready for other foods and when the necessary energy and nutrient needs for the infant cannot be met with only breast milk intake.[2] WHO explains complementary feeding as a timely, adequate, safe and appropriate feeding for the infant's consumption. Breast milk should be given within an hour of birth and for the first 6 months, breastfeeding is recommended without solid food or any liquid including water supplementation. To start complementary feeding after 180 days, which is the 6 months are complete, is appropriate and must be supported by breast milk until 2 or more. Children who are undernourished by breast milk have recurring infections and a decline in growth. It is stated that malnutrition is growing in many countries in 6-18 months, and the shortcomings in this age range are difficult to replace later during childhood.[3] The stunting rate, which is the result of chronic inadequate nutrition has risen to 9%, particularly between 18 and 23 months. The increase in this period is directly related to a long process covering the first 1000-day feeding period of the infant. That duration is closely related to nutrition during the pregnancy process, breast milk intake and

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the transition to adequate complementary feeding in time. Also, the weakness level is stated at 7% in 6-8 month-olds, so it is more common under the age of 1 year. This indicates the time when the nutritional value of the breast milk is inefficient to meet the amount of an infant's energy intake.[4]

The high rate of weakness, especially in children between 6 and 8 months, is a short-term indicator that the Turkish society does not give enough importance to complementary feeding practices, which must be supported by breast milk and should be started between these months. It was deduced from these malnutrition data that the importance of complementary feeding was not emphasized enough. For this reason, this review aims to state the current recommendations about the appropriate time to start complementary feeding, the contents of complementary foods, the consistency of complementary foods that the infant should take in accordance with the month, the amount and frequency of meals, and which foods should be avoided by infants until the age of 1 year, and to specify the importance of complementary feeding.

Age to Start Complementary Feeding of Infants

Complementary feeding is required when breast milk alone is deficient to meet all the nutritional needs of the infants from the sixth month. Complementary nutrients often have a lower nutrient quality than breast milk. Additionally, complementary nutrients can be delivered in insufficient quantities, replacing breast milk if delivered before or too often. Infants can consume as much food as their stomach capacity for each feeding. Repeated infections reduce appetite and increase the risk of inadequate intake.[3] Complementary feeding means nourishing the infants with other nutrients in addition to breast milk. Thanks to this process, the infant gradually gets used to family meals. When the infant is 2 years old, breast milk is replaced by family meals, and if the baby wants, mothers can continue to breastfeed.[2] Health benefits of breast milk are widely known, there are differing opinions on the appropriate duration of exclusive breast milk intake, without no additional solid food and no beverages, including water. Most of the recent disagreements in developed countries centre on micronutrient deficiency. In the systematic review of 23 studies, 11 of which were conducted in developing countries and the other 12 in developed countries; it has been suggested that in developing countries, newborns may have insufficient iron stores, and only breast milk intake without iron supplementation for 6 months may worsen the hematological status. Exclusive breastfeeding for 6 months has many advantages compared to complementary feeding in addition to breast milk after 3 or 4 months of exclusive breastfeeding. These advantages are; less risk of gastrointestinal infections, faster maternal weight loss after delivery, and a delayed menstrual cycle. No benefit has been demonstrated for 6 months of exclusive breastfeeding for tooth decay, obesity, allergic diseases, and cognitive and behavioural problems.[5] On the contrary, a review has claimed that an infant who is breastfed for longer than six months will have a better intellectual effect, a lower risk of developing attention deficit and a lower incidence of autism.[6] In a study in which infants fed exclusively-breast milk for the first six months were compared with infants fed only breast milk for the first four months and supplemented with solid food between four and six months.Exclusively breastfed infants have been shown to crawl earlier than solid-fed infants.[7] In a survey, it was shown that breastfeeding is significantly associated with reducing obesity and high body fat rates when the child reaches the age of 9-11 years old.[8]

Neuromuscular development is one of the most important characteristics during the transition to complementary feeding. Because it is stated that being introduced to different eating methods, such as eating with a spoon, plate or finger, both too early and too late, may have some harm in terms of the development of motor skills. Although there are no specific age ranges defined for complementary feeding, it is stated that neuromuscular development that will allow infants to be spoon-fed at approximately 5 months old. The European Food Safety Authority (EFSA) states that after the 4th month, the infant's digestive system is mature enough for the digestion and absorption of proteins and fats taken from a source other than breast milk. Simultaneously, after the 4th month, the infant's renal functions have matured significantly and the infant can cope with the high renal solute load. According to EFSA, starting complementary feeding after the 4th month does not pose a problem in terms of both the digestive system and kidney functions. In this view, when the baby completes its 4th month, when it is 17 weeks old, it is a suitable time to start complementary feeding.[9] It is asserted, that the ability to hold their head upright, move their eyes-hands-mouth with coordination in the form of look-take and put in the mouth swallow foods indicate that the infant is ready for complementary feeding.[10] There are various complementary nutrition practices from country to country. In Germany, it is advocated that complementary feeding should not be introduced at the beginning of the 5th month and should not be started at the beginning of the 7th month. In Denmark, it is proposed to launch at approximately 6 months and not before 4 months if complementary feeding is to be started early.[9]

If the infant is breastfed more or less than it should, this will affect its complementary feeding. The mother will not know how much breast milk she gives while breastfeeding her infant, and concurrently, she will not be able to calculate the energy amount of the food while feeding her with complementary foods. For this reason, it is necessary to follow the principles of sensitive supply.[1]

Contents of Complementary Nutrients

Infants should consume various foods to meet their nutritional fundamentals and meet different tastes and textures. A comprehensive diet includes breast milk, cereals, roots and tubers, legumes, nuts and seeds, dairy products, meat products, eggs, vegetables and fruits rich in vitamin A and other vegetables and fruits every day. It is more likely that infants fed a complementary diet of this variety can meet their needs in terms of micronutrients such as vitamin A, iron, calcium, thiamin, folate, zinc, vitamin B_6

and B_{12}.[11] Studies have demonstrated a significant relationship between low family income and inadequate nutritional diversity in complementary feeding.[12,13] The recommended daily energy amounts to meet the increased energy needs of infants are shown in Table 1.[14] Studies have emphasized that there may be some micronutrient deficiencies in the complementary feeding process.[15,16] It is asserted that in the 6-24 months period, a diet based on plant-based foods that are not fortified with supplements will cause some micronutrient needs of the infant. These micronutrients are shown as iron, zinc, calcium and vitamin B_{12}. For this reason, it is recommended to include red meat, poultry, fish and eggs as well as dairy products in the infant's diet.[17]

When starting complementary feeding at the 5th month, it is emphasized to give only vegetables for at least 2 weeks before adding fruit and rice. It is a consideration that not giving the infants a sweet taste in the first weeks, will increase its effect on vegetable purchases in the following periods. Although it is thought that this application will not cause a shortage of iron for infants who switch to complementary feeding between 4 and 6 months, it is recommended to include iron-rich foods for infants who will start complementary feeding after 6 months.[18] Although there is some evidence that infants consuming only vegetables during the first month increase their liking and intake of vegetables, there are very few studies on the permanence of this effect after infancy.[19]

There is a staple consumed by every society. Cereals such as rice, wheat and corn can be given as examples of these basic foodstuffs. They provide energy due to their starch content. Additionally, grains provide proteins. Due to phytates in grains, the absorption of iron, zinc and calcium they contain is inhibited. Fresh roots, such as potatoes contain vitamin C, and yellow-coloured sweet potatoes and corn are sources of vitamin A. To fill the energy and nutrient deficit in infants' complementary feeding, it is recommended that legumes such as peas, beans and oilseeds such as sesame seeds, foods of animal origin, dark leafy vegetables and orange fruits and vegetable oils should be given together with cereals.[2] In research conducted in South Africa, where the history of complementary feeding given by mothers to their infants was examined. It has been reported that the first food introduced to infants from the sixth month is a soft-consistent porridge made from corn. For infants in younger months, it has been stated that the porridge is made in a more watery consistency that can be drunk from a bottle. It was told that some mothers fed their infants with starchy vegetables such as pumpkin and potatoes, and corn porridge with gravy, especially at night.[20] Infants should be fed not only the sauce of the meals (gravy) but also the food itself.[21]

Legumes and oilseeds are good sources of protein but are deficient in vitamin A and vitamin C when dried. Some oilseeds and legumes such as soybeans and peanuts are rich in oil and therefore have high energy content. It contains phytate, which inhibits the absorption of iron, calcium and zinc in legumes and oilseeds such as cereals. In addition to phytates, most raw peas and legumes contain several other non-nutritive elements that prevent the body from using nutrients. Many of these non-nutrients are destroyed by cooking, but phytates cannot be destroyed. Soaking legumes and pouring the water before cooking helps remove non-nutrients and reduce phytate content. Animal food is rich in several nutrients but expensive. Eggs, cheese, yoghurt, milk and red meat are good sources of protein. Iron, vitamin A, and folate are found in the liver, and even a small fraction of it provides many nutrients. Egg yolk is rich in vitamin A and iron content is also high, but its absorption of iron is low. Butter is rich in vitamin A.[2] Dairy products are the richest sources of calcium. If dairy products are not consumed enough in the diet, other relatively calcium-rich foods, including small fish, soybeans, cabbage, carrots, zucchini, dark leafy vegetables and pumpkin, should be given in the infant's diet.[17] Vegetables and fruits such as carrots, pumpkins mangoes, which are yellow-orange, and green leafy vegetables such as spinach, are rich in carotene and vitamin C.[21] Meat and fortified infant cereals are important sources of essential nutrients.[22]

From the 6th to the 12th month, the energy content of the diet from fat should be 40%. 4% of the energy should come from linoleic acid (LA), 0.5% from alpha linolenic acid and 100 milligrams per day from docosahexaenoic acid (DHA).[23] Fats are a source of energy in the diet for infants. One teaspoon of vegetable oil or fat gives additional energy to the meal.[2]

There is no evidence of the order and speed in which complementary foods should be introduced, it is generally recommended to try solid foods individually, at intervals of 2-7 days.[22] In Table 2, appropriate complementary food choices and example recipes for meals are given according to the infant's months.[10,19,24-29]

Meal Frequency in Complementary Nutrition

The meal frequency of complementary feeding in infants in addition to breast milk intake, that is recommended 2-3 meals a day for 6-8 months old, 3-4 meals for 9-11 months old. For 12-24 months old, it is advised to offer nutritious snacks 1-2 times a

Table 1. Energy content of complementary feeding by month[14]

Infant's age in month	Average required daily energy from breast milk by month	Average required daily energy from complementary feeding by month	Average required total energy by month	Number of meal frequencies containing 0.80 kcal per gram
6-8 Months	413 kcal/day	202 kcal/day	615 kcal/day	2-3 meals
9-11 Months	379 kcal/day	307 kcal/day	686 kcal/day	At least 3 meals
12-23 Months	346 kcal/day	548 kcal/day	894 kcal/day	At least 4 meals

Table 2. Appropriate complementary food choices and example recipes for meals are given according to the infant's months[10,19,24-29]

Infant's months	Appropriate food groups[10,24-27]	Recipes by months[28,29]
4 to 6 months (Weeks 1-2)[19]	Vegetables	Launch complementary feeding with single vegetables. Cut the vegetables into small pieces and boil them in a small amount of water or stem them until they are soft. Mash with a fork until smooth lump free puree. If it is too thick, add a little breast milk or infant formula. Serve warm or chilled not hot. Use little, shallow and plastic spoon. Begin with 2 to 3 little spoons or 4 to 6 little spoons of vegetable puree, gradually increase the amount. **Recipes for Breakfast and Lunch:** "1 vegetable for every trying." Broccoli puree, Zucchini puree, Carrot puree, Green bean puree, Spinach puree, Cauliflower puree, Potato puree.
4 to 6 months (Weeks 2-3)[19]	Vegetables	Mix the vegetable puree. You may use unsalted butter or olive oil for puree. **Recipes for Breakfast and Lunch:** e.g.Leek and potato and carrot puree, e.g.Carrot and cauliflower, and sweet potato puree, e.g.Potato and carrot and broccoli and cauliflower puree.
Around 6 months	-Vegetables, -Fruits, -Meats, -Wholewheat bread, oatmeal, rice -Pasteurised Full-fat yoghurt, -Pasteurised full-fat cheese unsalted, -**Cow's milk or other animal milk resources (goat's or sheep's milk) may be used in cooking. -Fats (olive oil and unsalted butter)	Use protein sources in the thicker puree or mashed foods or soups. Mix the vegetable puree and soup with mashed beef, lamb, chicken, turkey, fish (no bones), egg. Soft ripe fruits can be given by mashed, harder fruits should be given by cooking or by grating on a glass grater. Eggs should not be used raw or lightly cooked. Start with a small amount of egg yolk. If tolerated, increase the amount gradually. Additionally, finely grounded nuts, peanut, or other nut butters can be given for 6 months of age if there is no history of allergy. If torelated, these foods can be part of infant's daily diet. EFSA states that gluten should be introduced to infants between 4 and 12 months. **Recipes For Lunch:** e.g.Chicken and potato and carrot thicker puree e.g.Full-fat Pasteurized cheese with thicker vegetable puree. e.g.Vegetable soup with meat and bread crumb e.g.Full-fat yoghurt and thicker vegetable puree e.g.Fruit puree and breast milk or formula e.g.Fruit puree and cereals with breast milk or infant formula.

Table 2. Continued

Infant's months	Appropriate food groups[10,24-27]	Recipes by months[28,29]
7-9 months	-Vegetables -Fruits, -Meats, -Wholewheat bread, oatmeal, rice, pasta -Pasteurised full-fat yoghurt, -Pasteurised full-fat cheese unsalted, -**Cow's milk or other animal milk resources (goat's or sheep's milk) may be used in cooking. -Fats (olive oil and unsalted butter)	Move on to Lumpy and Soft Finger Foods. Examples for Soft Finger Foods: Cooked vegetables, Soft ripe fruits, Finger of bread, Stick of pasteurized cheese. Lentils, beans, chickpeas can be added to the meal plan. Boiled and peeled off, then added to soups and meals by mashed. A well-cooked whole egg can be started to be given if tolerated by the infant. **Recipes for Breakfast:** e.g. Porridge (cooked with whole milk) served with yoghurt and finger fruit e.g. Scramble egg serves with finger wholewheat bread and heated and softened tomatoes. **Recipes for Lunch:** e.g. Pasta with meat (mashed until lumps) and boiled or stem finger vegetables e.g. Lentil soup (mashed until lumps) with finger wholewheat bread e.g. Rice with meat (mashed until lumps) and served with boiled or stem finger broccoli and full-fat yoghurt. e.g. Cooked fish (haddock fillet) in the oven and cooked vegetables (mashed until lumps) served with finger smaller pasta shapes. e.g. Boiled pulses and add full-fat cheese (mashed until lumps) serve with boiled finger vegetables and full-fat yoghurt **Mid-afternoon Meal:** e.g. Finger pear slices with full-fat yoghurt e.g. Semolina with whole milk added banana (mashed until lumps) serve Finger peach slices
10-12 months	-Vegetables -Fruits, -Meats, -Wholewheat bread, oatmeal, pasta, couscous, -Pasteurised Full-fat yogurt, -Pasteurised full-fat cheese unsalted, -**Cow's milk or other animal milk resources (goat's or sheep's milk) may be used in cooking. -Fats (vegetable oils and unsalted butter)	**For Breakfast:** e.g. Scramble eggs with small pieces of finger vegetables and finger bread with fat spread e.g. Egg veggie omelet with finger bread with fat spread and full-fat pasteurized cheese e.g. Porridge cooked with whole milk and fruit serve with finger banana stick and full-fat yoghurt **For Lunch:** e.g. Small pieces of red meat with rice and finger stem broccoli e.g. Chicken breast with finger wholewheat bread and full-fat yoghurt e.g. Tuna mixes well with full-fat yoghurt and served with finger carrot and finger-boiled potato e.g. Turkey with Cous Cous serves full-fat yoghurt **Mid-afternoon Meal:** e.g. Cooked apple and apricot in the oven with added cinnamon serve with full-fat yogurt e.g. Semolina with whole milk add cinnamon and mix with heated finger apple **Recipes for Dinner:** e.g. Lentil soup with finger bread e.g. Finger chicken with full-fat yoghurt

*Each meal time, offer water to your infant from an open cup.[29]

**Cow's milk or other animal milk resources (goat's or sheep's milk) may be used in cooking or mixed with food, but it should not be used as the main food or drink until your infant is 12 months old[10]

day in addition to 3-4 meals.[3] If the infant is not breastfed or the energy content of the receives is about 0.60 kcal per gram, the frequency of meals given to the infant should be increased.[21]

Number of Complementary Nutrients

One of the most important points to be considered in the complementary feeding of infants is the stomach capacity of infants.[11] The gastric capacity of newborns is quite limited and varies between 38 and 76 mL.[30] The normal pre-retching stomach capacity for infants is deemed 20 mL per kg of a standard meal.[31] It has been stated that the meals of babies aged 6-8 months can vary between 160 and 200 grams.[9] The stomach capacity of an infant is 30 mL per infant's body weight kilograms (kg), and it is stated that the stomach capacity of an infant with an average weight of 8 kg will be 240 mL, which is approximately equivalent to one large glass.[21]

Infants have a limited stomach capacity, they should be fed a small number of rich meals at each feeding. In the first introduction to complementary feeding, infants should start with small amounts of food and gradually increase the amounts as the baby grows. When introducing complementary foods to infants, it is proposed to start with 2-3 teaspoons first, then increase the infant's intake considerably, and feed the infant to take half of a 250 mL bowl at each meal between the 6th and 8th months. Between the 9th and 11th months, it is prescribed to ensure that the infant receives half of a 250 mL bowl at each meal, and in the 12th and 23rd month, it is recommended to start with ¾ of a 250 mL and then feed one bowl at each meal.[11]

Consistency in Complementary Nutrients

The consistency of complementary foods should be increased slowly from soft to semi-solid to solid consistency, considering the abilities and needs of babies. An infant should transition from pureed foods to finger foods and then family foods until they are 1 year old. Consumption of complementary foods in a puree consistency for prolonged periods may delay the consumption of foods of various textures and consistencies in infants.[11]

Infants should be introduced to complementary foods in the form of smooth puree and with the help of a spoon between the fourth and 6th months. Between the 6th and 9th months, it is recommended that family meals of different tastes and textures be crushed or lumped together and that infants are encouraged to feed themselves with finger foods made of cooked vegetables and soft ripe fruits. Between the 9th and 12th months, it is recommended to support the diet given to infants during the day with 3 main meals.[10] It is stated that not introducing infants to foods such as hard fruits and meat that require chewing at the recommended age ranges may create limitations in terms of diversity and texture in their diets in the future. It has been shown that infants fed with lumpy foods for the first time after 10 months have more feeding problems at 15 months compared to those introduced at 6 and 9 months.[32]

A thin consistency of porridge and soups causes the infant to take less energy.[11] Instead of a liquid meal like soup; it is recommended to crush the grains, legumes and vegetables added to the soup to a thick consistency and add oil to the mixture for additional energy. When preparing porridge made with cereals that are suggested some or all of the water added to the porridge can be replaced with whole milk and some oil can be added for a softer consistency.[2]

Nutritional Supplements A Baby Should Take According to Months

Vitamin K levels are low at birth and decrease within the first few days of life. Classical forms of hemorrhagic diseases such as bleeding in the gastrointestinal tract, circumcision area, or umbilical cord occur in the first weeks of life, especially on the 2nd and 4th days of life, in a few infants who do not receive vitamin K at birth. Therefore, postnatal vitamin K injection is desired for all infants.[33] Between 1961 and 1993, the American Academy of Pediatrics recommended a dose of 0.5-1 mg parenterally or 1-2 mg orally for early postnatal vitamin K protection. In 2003, an intramuscular injection of 1 mg of vitamin K was recommended as a standard for newborn healthy infants.[34]

Dietary sources of vitamin D are rare. It is mostly found in oily fish such as wild salmon, mackerel, eel, anchovy, sardines, swordfish and tuna, and to a lesser extent in egg yolk and some mushrooms. Since vitamin D is synthesized from the skin by sunlight, adequate outdoor activities are recommended in daylight. A review suggested an oral supplement of 400 IU of vitamin D daily for all infants throughout their first year of life.[35]

In the Iron Like Türkiye (2004) program, term babies are usually born with sufficient iron stores for their first 4-6 months. After this process, it is stated that the iron stores of the infant decrease gradually according to the changing feeding plans. For this reason, all babies should be screened for iron deficiency anaemia and 1mg per kg iron preparation should be given once a day until one year old to support infants aged 4-12 months without anaemia. That is offered to every infant aged 4-24 months with anaemia should be treated with an iron preparation of 3 mg per kg once a day for 3 months. Iron support should be continued until the age of 1 year after the anemia is resolved. The preparation of irons should be given when infants are hungry, not to be given with foods containing milk and milk products If a dairy product is consumed, a period of at least half an hour must pass. The taste of iron preparations is not very suitable for infants, and vitamin C increases the absorption of iron so preparations may be taken with foods and beverages containing vitamin C.[36] In the review where the recommendations of Swiss experts are presented, the amount of iron mineral is stated as 2-3 mg per kg for Fe^{+2} and 3-5 mg per kg for Fe^{+3} mineral.[37]

The Role of Foods with Allergic Risk in Infant Nutrition

Currently, according to international guidelines, it is stated that the introduction of allergic foods such as eggs and peanuts does not

need to be postponed after 4-6 months.[38] In the Enquiring About Tolerance study, there were declared two groups: the experimental group and the other one control group. The experimental group consisted of healthy 3- to 4-month-old infants without risk of allergy and the control group consisted of not at risk of allergy infants who were breastfed only for 6 months. In study 6 allergenic foods which were defined as cow's milk, peanuts, eggs, sesame, fish and wheat were tested. When each group reached the age of 3 years old the frequency of allergy development in children who were introduced to allergic foods in the early period was declared 5.6% and the other group who were introduced to allergic foods at 6 months of age was asserted 7.1%. It was shown that the frequency of egg and peanut allergies decreased significantly in the experimental group, which was introduced in the early period. There was no difference between the experimental group and the control group in terms of the frequency of milk, sesame, fish and wheat allergies.[39]

Responsive Feeding

Responsive feeding requires establishing a reciprocal relationship between infants and those who feed them. It includes infants' hunger and satiety signals, people who care for babies recognize these signals, people respond to these stimuli in an appropriate, nurturing and quick way, and the infant experiences the attention of the person who takes care of it. Responsive feeding helps infants develop self-control in their food intake and transition to self-feeding.[11] While infants are fed by sensitive feeding principles; they should be fed slowly and patiently. Those who feed infants should encourage them to eat, but not force them. If infants refuse many foods, the same food should be tried in different tastes and textures, and eye contact should be established and spoken with infants during feeding.[17]

Introducing Infants to Gluten and Foods Babies Should Avoid up to One Year Old

In a survey, high sugar intake in infants at the age of 1 year was associated with increased weight gain in the following months.[40] It is recommended not to add salt and sugar to complementary foods, to reduce the amount of sugar from fruit juices, and to avoid sugar-sweetened beverages. Fennel tea and fennel oil are not recommended for children under 4 years of age.[41] Honey is a resource for *Clostridium botulinum* toxins that causes infant botulism in babies younger than one year of age.[42] Many infant botulism poisoning cases have been reported in the literature in Europe and America.[43-46] Thus, honey should not be given before the age of one year due to the risk of infant botulism.[41] In studies evaluating the effect of introducing gluten to infants on the risk of celiac disease, it has been reported that early introduction of gluten is not associated with the risk of developing celiac disease[47] but a late introduction to gluten is associated with late onset of the disease.[48] The infant can be introduced to gluten when the complementary food is switched between 4 and 12 months. It has been shown that excess gluten should be avoided in the first weeks of introduction.[41]

The Amount of Fluid That Infant Should Take by Months

High protein intake of infants, 20% of the energy coming from protein in the diet, can seriously disrupt their water balance, especially when extrarenal water losses increase or they do not take any other fluids.[49] 6-24-month-old non-breastfed infants who are living in a temperate climate should take at least 400-600 ml fluid in addition to approximately 200-700 ml fluid from milk and other nutrients. Infants who are living in hot climates are recommended to take an additional 800-1200 ml fluid.[17] It is recommended that infants sip water instead of sweet drinks such as fruit juice, which can cause tooth decay while taking complementary foods.[29]

CONCLUSION

Malnutrition data has shown by recent population and health surveys in Turkish society's new generation, who will form our future do not have an adequate and balanced nutrition history. The importance of detecting malnutrition among children as soon as possible with frequent screening is obvious. Mild malnutrition is a situation that should be recognized in a short time and supported by adequate and balanced nutrition practices. It is distinct that complementary feeding practices are an extremely important building block for the health of the next generation. For plans, it should be aimed to emphasize the significance of complementary feeding with the training given by dietitians to pregnant women and the training to be carried out in health centres or public education centres to raise awareness among health workers and the public on complementary feeding.

Ethics

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Original Article

The Neglected Disease of Modern Society: Trauma. Outcomes and Prognostic Factors for Pediatric Trauma Patients in PICU

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ABSTRACT

Objective: In this study it was aimed to investigate the demographic and clinical characteristics of pediatric trauma patients requiring follow-up in Pediatric Intensive Care Unit (PICU) and to contribute the data in this field by assessing the outcomes and prognostic factors.

Methods: This retrospective, observational study was carried out in the 12- bed medical PICU. We reviewed the clinical records of all trauma patients.

Results: A total of 99 patients (61 males and 38 females) were enrolled in this study. Eight patients died and the mortality rate was found as 8%. In univariate logistic regression analysis, presence of brain edema was associated to 12 folds increase in the mortality [Odds ratio (OR): 12; 95% confidence interval (CI): 2.23-64.48]. Presence of subarachnoid hemorrhage (SAH) was associated to 15 folds increase in the mortality (OR: 15; 95% CI: 2.75-81.58). Pediatric trauma score (PTS)<8 was associated to 1.17 folds increase in the mortality (OR: 1.17; 95% CI: 1.05-1.31). In the multivariate logistic regression analysis presence of brain edema was associated to 6,492 folds increase in the mortality (OR: 6,492; 95% CI: 1.078-39.06) and presence of SAH was associated to 8.68 folds increase in the mortality (OR: 8.68; 95% CI: 1.451-51.933).

Conclusion: The Glasgow coma scale score, PTS score and presence of SAH and brain edema are the factors effective on mortality in PICU.

Keywords: Trauma, child, PICU

INTRODUCTION

Although there have been improvements in supportive care in pediatric intensive care (PICU), trauma continues to be the leading cause of death and acquired disability among children. It has been reported that over 1 million children die due to trauma annually worldwide.[1] In 1966, a special report by the American National Academy of Sciences defined trauma as the "neglected disease of modern society".[2] United States (US) data shows treatment costs exceed 20 billion dollars annually in pediatric trauma cases. In addition, while the mortality rate is 1.9:1000 in leukemia, commonly seen in the pediatric age group, 10 of 100,000 child dies due to trauma every year.[3] These data demonstrate that trauma is a severe public health issue in childhood.

Mechanisms and types of injury depend on age, anatomy, environment, and children's interest. The most common causes of traumas are falls, motor vehicle accidents, pedal cyclist accidents, drowning, burns, and child abuse. Injuries with severe or multi-trauma requiring a high level of care are followed in the PICU. Many studies reported on adult trauma patients' outcomes treated in intensive care units in the literature. However, pediatric

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trauma cases have distinct vital signs and clinical problems, and there are few studies about trauma patients treated in PICUs. Therefore, outcomes and risk factors associated with mortality in PICU are needed to establish the optimal clinical management of pediatric trauma patients.

The present study aimed to investigate pediatric trauma patients' demographic and clinical characteristics requiring follow-up in PICU and contribute the data in this field by assessing the outcomes and prognostic factors.

MATERIALS AND METHODS

This retrospective, observational study was carried out in the 12-bed medical PICU of the Erciyes University Children Hospital in Kayseri. The clinical records of all trauma patients were reviewed. The study included 99 patients with available data. The following information was abstracted from the medical charts of the patients: age (1 month-18 years), gender, Glasgow coma scale (GCS), mechanism of injury, seasonal distribution, injured body region, type of injury, therapeutic interventions (positive inotropic support, mechanical ventilation (MV), MV day, blood transfusion), length of PICU stay and outcome (survivors vs. nonsurvivors). Patients were categorized into three groups to define the severity of traumatic brain injury (TBI) based on the initial GCS as follows: mild TBI (GCS: 13-15), moderate TBI (GCS: 13-8), and severe TBI (GCS<8). According to the pediatric trauma scores (PTS), patients were also divided into two groups: severe (PTS≤8) and mild (PTS >8). By Helsinki Declaration, the study was approved by the Ethics Committee on Clinical Research of Erciyes University, Medicine School (approval#2018/501). Informed consent forms were obtained from parents.

Statistical Analysis

Statistical Package performed statistical analyses for Social Sciences (SPSS) version 22.0. The Shapiro-Wilk test assessed normal distribution. Variables with skewed distribution are summarized as median and interquartile ranges, while categorical variables are summarized as count and percent (%). In binary group comparisons, the Mann-Whitney U was used to compare variables with skewed distribution, while the chi-square test was used to compare categorical variables. Pairwise correlation tests were used to assess relationships among variables. Univariate logistic regression analysis was performed to determine gender, brain edema, epidural hematoma, subdural hematoma, subarachnoid hemorrhage (SAH), and PTS<8 on mortality, while multivariate logistic regression analysis was performed to assess the combined effects of SAH and brain edema. A p-value<0.05 was considered statistically significant for all comments.

RESULTS

Ninety-nine patients (61 males and 38 females) were enrolled in this study (Table 1). The median age was 62 months (33-115). Eight patients died, and the mortality rate was found as 8%, lower than the yearly overall PICU mortality rate (16%) (p<0.001). The study population was categorized according to GCS, and it was detected that 41 cases (41.4%) with mild TBI, 41 cases (41.4%) with moderate TBI, and 17 patients (17.2%) with severe TBI. The study population detected a significant relationship between mortality and severe TBI (p<0.001).

Survivors and non-survivors were assessed by the Pediatric Risk of Mortality Score III (PRISM III). It was found that the PRISM III score was 5 (2-11) among survivors and 38 (21-48) among non-survivors (p<0.001).

The most common trauma type was out-of-vehicle traffic accidents. When non-survivors were assessed according to trauma type, it was found that 4 patients died due to out-of-vehicle traffic accidents, 2 patients due to in-vehicle traffic accidents, one patient due to crush injury, and one other due to drowning (Table 1).

Table 1. The evaluation of demographic characteristics and trauma types of the cases

Variable	N	%
Gender		
Male	61	61.6
Female	38	38.4
Glaskow Coma scale (GCS)		
GCS: 13-15	41	41.4
GCS: 13-8	41	41.4
GCS: <8	17	17.2
Pediatric trauma score (PTS)		
PTS>8	67	67.7
PTS≤8	32	32.3
Outcome		
Survivor	91	92
Non-survivor	8	8
Mechanism of injury		
Pedestrian	30	30.3
Vehicle	17	17.2
Fall	28	28.3
Crush	9	9.3
Press	3	3
Drowning	7	7.1
Electric shock	1	1
Gunshot injury	2	2
Hanging	2	2
	Median (25-75)	p-value
PTS		
Survivor	7.5 (5-99	<0.001
Non-survivor	0.5 (-0.75-4.75)	
Pediatric risk of mortality score III		
Survivor	38 (31-48)	<0.001
Non-survivor	5 (2-11)	

The patients were assessed according to the PTS, and it was found that 32 cases (32.3%) were in the mild trauma group, and 67 cases (67.7%) were in the severe trauma group. The median PTS value was 7 (5-9), while it was 7.5 (5-9) in survivors and 0.5 (-0.75-4.75) in non-survivors (p<0.001) (Table 1). In addition, in all non-survivors, PTS was found ≤8. In terms of mortality, there was a significant relationship between groups (p=0.035). The median value of the PRISM III score was 10 (3-21) in patients with PTS≤8, whereas 2 (1-8) in patients with PTS>8 (p<0.001). In addition, GCS showed a significant, negative correlation with PTS and PRISM III (r=-0.688, p<0.001 and r=-0.588, p<0.001, respectively) (Table 2).

The median length of PICU stay was 3 days (1-5). It was found that the length of PICU stay was negatively correlated with GCS and PTS scores (r=-0.235, p=0.020 and r=-0.392, p<0.001, respectively). Table 2 presents correlation coefficients among variables evaluated.

Forty-three patients (43.4%) required intubation, and the mean length of stay on MV was 2 days (2-4). The intubation was required in 7 (17.0%) of 41 patients with mild TBI, in 22 (53.0%) of 41 patients with moderate TBI, and 14 (82.0%) of 17 patients with severe TBI (p<0.001). The relationship between the requiring intubation and PTS score was assessed, and it was found that intubation was needed in 40 (60%) of 67 patients with severe trauma and 3 (9%) of 32 patients with mild trauma (p<0.001).

The highest number of admission was observed in August (and=17; 17.2%), while the lowest number of admission was observed in February (n=1; 1%) (Figure 1).

The head was the most commonly involved region of the body (62%), followed by extremity injury (17%), chest (33%), and abdomen (13%).

Diffuse axonal injury was detected in 11 patients (11.1%); including one patient with mild TBI (2.4%), 6 patients with moderate TBI (14.6%) and 4 patients (23.5%) with severe TBI (23.5%) (p=0.431). Brain edema was detected in 24 patients (24.2%); 3 patients with mild TBI (7.3%), 12 patients with moderate TBI (29.3%) and 9 patients with severe TBI (52.9%) (p=0.001). In univariate logistic regression analysis, brain edema was associated with 12 folds increase in mortality [Odds ratio (OR): 12; 95% CI: 2.23-64.48]. It was found that the presence of subarachnoid hemorrhage (SAH) was associated with 15 folds increase in the mortality (OR: 15; 95% CI: 2.75-81.58) while PTS<8 was associated with 1.17 folds increase in the mortality (OR: 1.17; 95% CI: 1.05-1.31). In the multivariate logistic regression analysis, it was found that the presence of brain edema was associated with a 6,492 folds increase in the mortality (OR: 6,492; 95% CI: 1,078-39.06), while the presence of SAH was associated with 8.68 folds increase in the mortality (OR: 8.68; 95% CI: 1,451-51,933). Table 3 presents logistic regression analysis results regarding risk factors influencing mortality.

Table 2. Correlation coefficients between variables

	PRISM III	Length of PICU stay
Pediatric trauma score	- 0.588*	- 0.392*
Glasgow Coma scale	-688	- 0.235

*In these correlations, p<0.05
PRISM III: Pediatric risk of mortality score III, PICU: Pediatric intensive care

It was found that 12 patients (12.1%) experienced seizures during follow-up, while 3 patients (3%) underwent tracheostomy. Surgery was performed in 22 patients (22.2%). In addition, blood transfusion was performed in 23 patients. Of the patients received blood transfusion, 20 patients (86%) were discharged while 3 patients died (14%) (p=0.334). Inotropic support was initiated in 4 cases, all of which died (p<0.001).

DISCUSSION

Trauma is a significant health issue due to resultant mortality and morbidity, in which incidence increases due to technological advances and violent events. It causes work labor loss and social and economics, as it more commonly affects the younger population in particular.

It is crucial to record trauma data to compare care and clinical outcomes across healthcare facilities. The present study is one of the few on pediatric trauma patients needing PICU admission. In this study, we have evaluated the data of 99 trauma patients to identify the prognostic factors that affect the outcome of the disease.

The frequency of trauma can be affected by several factors such as age, gender, year's season, time of day, and development level of the countries.[4] In our study, the male: female ratio (1.6) favored males, agreeing with the literature.[5] A higher frequency of trauma in boys may be attributed to more errant and aggressive behaviors. When seasonal distribution was assessed, it was seen that trauma cases most commonly occurred during June, July, and August (Figure 1). This may be because our province is at the crossing of important tourism centers with substantial migration and agricultural labor during summer. Our results have proven that males are more commonly injured in pediatric traumas and that traumas most widely occur during summertime.[6] Traffic accidents account for the majority of cases presented with trauma. A study by Doğan et al.[7] suggested that traffic accidents are the most

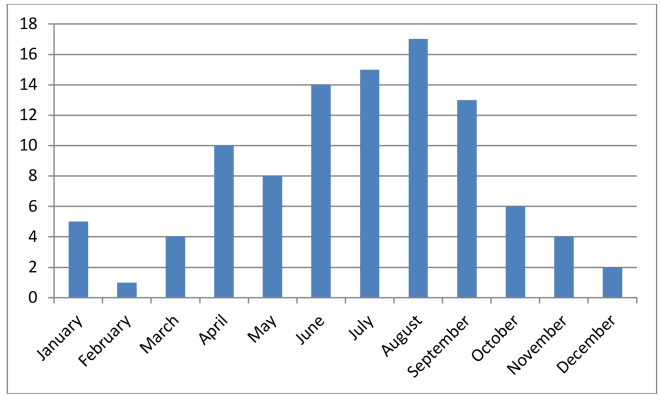

Figure 1. Distribution of the cases according to the months

Table 3. Logistic regression analysis of risk factors in pediatric trauma patients

	Univariate logistic regression			Multivariate logistic regression		
Variable	**p-value**	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**%95 CI**
Gender	0.938	1.06	0.212-4.195			
Brain edema	**0.004**	12	2.23-64.48	0.041	6.492	1,078-39.06
Subdural hematoma	0.798	1.24	0,23-6.67			
Epidural hematoma	0.644	1.69	0.182-15.79			
Subarachnoid hemorrhage	**0.002**	15	2.75-81.58	0.018	8.68	1,451-51,933
Pediatric trauma score <8	0.998	1.17	1.05-1.31			

CI: Confidence interval

important causes of trauma (23%). In a study on pediatric trauma cases presented to the emergency department, Akay et al.[8] found traffic accidents in 49%, falls in 31%, and other causes in 30%. Based on our results, it was seen that traffic accidents were a significant cause of PICU admission 48%. This may be because our facility is at the route of highways, and it is a center where most severe trauma patients are referred.

A variety of prognostic factors has been described in patients requiring PICU. Our study observed the highest mortality rate in patients admitted to a traffic accident. In their research, Doğan et al.[7] assessed the pediatric cases presented to the emergency department with trauma and found severe head injury in 9 of 10 non-survivors. In our study, there was a head injury in 7 of 8 non-survivors. Our results showed that head injury is the most crucial cause of PICU admissions and mortality. In addition, another remarkable finding in our study was that presence of brain edema and SAH significantly increased mortality.

In pediatric cases with trauma, intra-thoracic organ injuries are the second leading cause of mortality following central nervous system injuries. General mortality was 2-3% in trauma, while the mortality rate reached 20-30 in pediatric cases with chest trauma.[9] In a study on 507 patients with trauma, Gilles reported chest trauma in 30 (49%) of 61 non-survivors. In a study from Turkey, Akay et al.[8] reported chest trauma in 16 (70%) of 22 non-survivors. In our study, chest trauma was detected in 31 cases (32%), and 5 of 31 patients died (16%).

Several trauma scoring systems are developed to ensure the appropriate use of sources and reduce the mortality rate. GCS is a simple scoring system without testing, widely used to assess a patient's neurological status, and rapidly provides detailed information. It was shown that low GCS scores are associated with increased mortality.[10] In a study on 127 adult trauma patients admitted to ICU, Taşdemir et al.[11] suggested that the GCS score was lower among non-survivors. In our series, the results agree with previous studies. When patients were stratified according to GCS score, it was found that mortality was significantly higher while the length of PICU stay was significantly longer in patients with severe TBI in our study.

The PTS is another scoring system used in the follow-up of pediatric trauma patients, which was adapted from adult scoring systems. In a study by Tepas et al.[12], it was shown that there was a significant correlation between PTS and Trauma Severity Score.[13] In particular, it was concluded that PTS<3-4 was strongly associated with mortality.[14] In a study on 1658 patients who presented to the emergency department, Taş M et al. reported that PTS scores were higher in survivors when compared to non-survivors.[15] Similarly, Anıl et al.[16] said that hospitalization rate, need for ICU care, MV, blood transfusion, and mortality were significantly higher in patients with PTS scores ≤8. In our study, the PTS score was considerably lower in non-survivors. In addition, it was found that PTS was significantly correlated to the length of stay and need for intubation.

The Pediatric Risk of Mortality Score III (PRISM III) is a scoring system used to predict mortality in pediatric patients and assess the performance of Intensive care units (ICUs).[17] Gonçalves et al.[17] reported that PRISM III and Pediatric Logistic Organ Dysfunction (PELOD) scores are highly effective in predicting mortality. In a study from Turkey, Tekerek and Akyıldız[18], PRISM III score predicted mortality most effectively among scoring systems including PRISM, PELOD, and Pediatric Mortality index. In our study, the PRISM III score was significantly higher among non-survivors. In addition, our results showed a negative correlation between PTS and PRISM III.

Study Limitations

There are several limitations to this study. Limiting factors include the relatively small number of patients in the study group, and some data, such as time for PICU admission, time to achieve target serum osmolarity, and information about treatments used for patients with a brain injury was unavailable due to the retrospective study design. Another limiting factor includes evaluating all patients admitted for trauma, and creating a heterogeneous group. In particular, including patients without head trauma does not make it possible to consider prognostic factors for all trauma patients.

CONCLUSION

In conclusion, trauma most commonly involves males and occurs during summertime. Motor vehicle accidents are leading causes when assessed according to the type of injury. We want

to underline that the GCS score, PTS score, and presence of SAH and brain edema influence mortality in pediatric trauma patients. The presence of one or more aspects mentioned above can lead to increased mortality; thus, clinicians should be alert for such patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee on Clinical Research of Erciyes University, Faculty of Medicine (approval#2018/501).

Informed Consent: Informed consent forms were obtained from parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.D., S.Ö., B.N.A., Concept: A.D., S.Ö., B.N.A., Design: A.D., S.Ö., B.N.A., Data Collection or Processing: A.D., H.S.D., Analysis or Interpretation: A.D., S.Ö., B.N.A., Literature Search: A.D., H.S.D., S.Ö., Writing: A.D., S.Ö.

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Original Article

The Evaluation of Local and Systemic Reactions to Subcutaneous House Dust Mite Allergen Immunotherapy

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ABSTRACT

Objective: Allergen-specific immunotherapy is an effective treatment method that enables the development of immunotolerance against allergens in allergic rhinitis, asthma, and venom allergy. This study investigated the local and systemic reactions during subcutaneous house dust mite allergen immunotherapy.

Methods: Injection-related local and systemic reactions of 45 patients who received subcutaneous mite immunotherapy were evaluated retrospectively.

Results: Forty-five children, 15 (33.3%) females and 30 (66.4%) male were included in the study. A total of 582 injections were administered. A local reaction was observed in 23 (3.94%) of all injections and the systemic reaction was observed in only 1 (0.17%) injection. Sixteen (37.7%) of the children had local reactions during the immunotherapy process and 1 (2.2%) had a systemic reaction.

Conclusion: Although subcutaneous mite immunotherapy is a safe treatment, it should only be applied in centers with appropriate emergency equipment and trained healthcare professionals due to possible systemic reactions.

Keywords: Allergy, house dust mite, immunotherapy, local reaction, systemic reaction

INTRODUCTION

Allergen-specific immunotherapy (AIT) is a treatment method that provides immunotolerance by application of responsible allergens at specific doses and intervals.[1] It is an effective treatment for IgE mediated allergic diseases such as asthma, allergic rhinitis and venom allergy. Nowadays, AIT is available in subcutaneous, sublingual, oral, epicutaneous, and intralymphatic forms.[1,2] AIT is considered a safe treatment when performed in experienced centers and with appropriate indications. The most frequent side effects of AIT are local reactions such as edema or erythema, but systemic side effects could be observed.[2]

House dust mites (HDM), to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, are common indoor allergens and they are associated allergic rhinoconjunctivitis, allergic asthma, atopic dermatitis. Eighty-two different allergens from 10 different mite species have been identified.[3,4] In North and South America, Europe, Southeastern Asia, and Australia, 85% of the asthma cases showed HDM sensitivity and in middle China, this ratio is 91.1%.[3,5,6] About 50% of pediatric and adolescent asthma cases showed HDM allergen sensitivity.[7]

The effect of protective environmental measures is limited in HDM allergy and in most cases, additional treatment approaches are indicated. HDM immunotherapy is the most effective method in both asthma and allergic rhinitis treatment.[8-11]

This study aimed to evaluate the local and systemic side effects in the children with asthma or allergic rhinitis who received HDM subcutaneous immunotherapy (SCIT).

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MATERIALS AND METHODS

In this retrospective study, the medical records of the children diagnosed with allergic rhinitis or asthma who received SCIT for HDM and followed in the Pediatric Allergy Department between January 2020-January 2021 were evaluated. From the patient's records, demographic variables, clinical and laboratory findings were obtained. Also, adverse effects after SCIT applications were recorded. According to World Allergy Organisation recommendations, adverse SCIT reactions are classified into 2 categories; local and systemic reactions.[12] Systemic reactions can range in severity, from mild to life threatening anaphylaxis. Local reaction was defined as swelling, pruritus and redness at the injection site. Also, local reactions can be classified according to size and duration of occurrance. An extensive local reaction occurs when a local reaction develops at an injection site that is larger than the size of the patient's palm, and minor local reaction is smaller than as well. Induration developing within the first 30 min was accepted as an early local reaction, and induration developing after 30 minutes was considered a late local reaction.[12]

Eleven children were under antihistaminic prophylaxis before injection. They were prescribed antihistaminic due to previous history of recurrent local reactions.

HDM SCIT protocol applied according to the European Academy of Allergy and Clinical Immunology guidelines.[13]

Ethical board approval was obtained from the Institutional review board of the Uludağ University Faculty of Medicine (approval number: (2022-4/54 , date: 23.02.2022).

Statistical Analysis

All statistical analysis was performed using IBM SPSS for Windows, version 23 (IBM Corp., Armonk, NY). The mean, median, minimum, maximum, and standard deviation (SD) values were used to describe data. Kolmogorov-Smirnov normality test was used to analyze the distribution of data. Chi-square or Fisher's exact tests were used in the comparison of qualitative data. A p-value <0.05 was considered as statistically significant.

RESULTS

A total of 45 children, 15 (33.3%) females, and 30 (66.4%) males were included in the study. According to the skin prick test results of the patients, 33 (73.3%) were defined as monosensitized and 12 (26.4%) were polysensitized. Thirty-eight (84.4%) of the patients were receiving HDM SCIT only and 7 (15.6%) had multiple SCIT in the form of HDM and pollens.

A total of 583 injections were administered. Local reactions were observed in 23 (3.94%) of all injections 21 early local reactions, 1 early large, 1 late large local reaction and 1 (0.17%) systemic reaction.

Four (1.16%) local reactions were observed in 344 injections of the build-up phase. Nineteen (7.9%) local reactions were observed in 239 injections of maintenance phace. Only one systemic reaction was observed in the maintenance phace of SCIT (Table 1).

According to the gender of the children, late minor local reactions were more common in females than in males (p=0.004) (Table 2). The local reaction frequency was significantly lower in children using antihistamine prophylaxis (Table 3). The frequency of reactions was similar in children with and without asthma, allergic rhinitis, and conjunctivitis.

During the immunotherapy, 17 (37.7%) of the children had local reactions and only 1 (2.2%) had a systemic reaction. One child with asthma had a systemic reaction with a sudden onset of shortness of breath and bronchospasm 10 min after the administration of SCIT.

Eleven children were under antihistaminic prophylaxis before injection. Of those, two had early minor, one of them had late minor, and 2 had late extensive local reactions. Thirty-four patients did not require antihistamine prophylaxis.

DISCUSSION

Allergen immunotherapy is defined as "the only treatment method that can change the natural course of allergic diseases".[14] In SCIT, mild-to-moderate systemic reactions occur in approximately 0.1% of patients, while severe reactions are rare (1 in 1 million injections).[6]

In the previous studies, local reactions were reported in 5.2% to 82% of patients during the immunotherapy process, and systemic reactions were reported between 0.06% and 3.2%.[15-18] studies conducted in Turkey reported that local reactions occur in 0.38-4% of all injections and systemic reactions occur in 0.1% to 0.2%.[19,20] In a study evaluating HDM SCIT injection in children,

Table 1. The frequency of reactions after injection

Immunotherapy phases	Number of injection n (%)	Local reaction n (%)	Systemic reaction n (%)
Build-up	344	4 (1.16%)	0
Maintenance	239	17 (7.9%)	1 (0.4%)
Total	583	23 (3.94%)	1 (0.17%)

Table 2. Distribution of patients who had local and systemic reactions by gender

	The number of patient		
Type of reaction	**Female**	**Male**	**p-value**
Early minor local reactions	0	2	-
Early extensive local reaction	0	0	-
Early systemic reaction	1	0	-
Late minor local reaction	9	4	**0.004**
Late extensive local reaction	1	1	0.55
Late systemic reaction	0	0	-

Table 3. Distribution of patients who had reactions according to being under antihistamine prophylaxis			
Type of reaction	**Under antihistamine prophylaxis (n=11)**	**Not under antihistamine prophylaxis (n=34)**	**p-value**
Early minor local reactions	2	0	-
Early extensive local reaction	0	0	-
Early systemic reaction	0	1	-
Late minor local reaction	1	12	**0.040**
Late extensive local reaction	2	0	-
Late systemic reaction	0	0	-

3.5% local and 0.1% systemic reactions were observed. Most of the systemic reactions were associated with the respiratory system.[21] Sasihüseyinoğlu et al.[22] reported the data of 303 patients who underwent SCIT with a local reaction developed in 54 (17.8%) patients and systemic reaction in 4 (1.3%) patients. Local reactions were more common in those receiving HDM SCIT (20.6%) than in those receiving grass pollen immunotherapy (16.7%). Additionally, systemic reactions have been reported only in HDM SCIT.[22] Consistent with the literature, in our study, local reactions were observed in 23 (3.94%) of all injections and systemic reactions were observed in 1 (0.17%). A systemic reaction was observed in a patient during the maintenance phase.

Various studies support the idea that the individual dose of AIT after an extensive local reaction cannot predict the development of systemic reactions. However, there is no evidence that local reactions precede to systemic reactions.[15,23] The rate of extensive local reaction was found to be almost four times higher in patients who experienced a systemic reaction compared to those who did not experience any systemic reaction.[24] Systemic reactions are generally encountered during dose escalation (especially in "rush," and "clustered" protocols) and mostly non-fatal reactions. Most post-injection systemic reactions occur within the first 30 min. Therefore, patients are expected to wait for at least 30 min after subcutaneous administration.[1,25]

The principal limitation of this research was that the limited number of patients makes it difficult to provide a definite interpretation. In particular, the findings of this study should be interpreted with caution since they cannot be used to infer causality because of the study design.

CONCLUSION

HDM SCIT is the only treatment modality that can provide a cure for many years for treating asthma and allergic rhinitis. After SCIT injections, patients should be observed for at least 30 min in terms of local and systemic reactions. According to the knowledge gain from this study, systemic reactions are unpredictable so AIT should be administered by an experienced allergy specialist in a setting that permits the prompt recognition and management of adverse reactions.

Ethics

Ethics Committee Approval: Ethical board approval was obtained from the Institutional Review Board of the Uludağ University Faculty of Medicine (approval no: 2022-4/54, date: 23.02.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Z.K., Ş.Ç., Y.H.Ş., Y.C., N.S., Design: Z.K., Ş.Ç., Y.H.Ş., Y.C., N.S., Data Collection or Processing: Z.K., Ş.Ç., Y.H.Ş., Y.C., N.S., Analysis or Interpretation: Z.K., Ş.Ç., Y.H.Ş., Y.C., N.S., Literature Search: Z.K., Ş.Ç., Y.H.Ş., Y.C., N.S., Writing: Z.K., Ş.Ç., Y.H.Ş., Y.C., N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Therapeutic Plasma Exchange for Treating Pediatric Neurological Diseases

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ABSTRACT

Objective: Therapeutic plasma exchange (TPE) is performed in various neurological, hematological, renal and autoimmune diseases. This study was conducted to determine the indications, efficacy, safety and complications of TPE in pediatric autoimmune neurological diseases.

Methods: In this study, patients who were hospitalized in the pediatric intensive care unit of a tertiary university hospital between January 2017 and December 2021 and underwent TPE due to neurological diseases were evaluated retrospectively.

Results: A total of 20 patients were included in the study. Their ages ranged from 6 to 237 months, with a mean age of 63.16±183.12 months. Neurological TPE indications of the patients were autoimmune encephalitis (50%, n=10), Guillain-Barre Syndrome (45%, n=9) and Acute Demyelinating Encephalomyelitis (6.7%, n=1), respectively. Catheter occlusion was observed in 2 (10%) patients, allergic reaction in 1 (5%) patient, and hypotension in 1 (5%) patient as complications of TPE. Muscle strength of patients with GBS was evaluated according to the Medical Research Council scale before transfer to the service. It was determined that the score increased from 0 to 1 in two patients, from 0 to 3 in three patients, and from 1 to 5 in four patients. In 9 of the patients diagnosed with encephalitis, regression of acute phase reactants and improvement in neurological evaluation were observed.

Conclusion: When TPE is applied with appropriate indications and by an experienced team in pediatric neurological diseases, treatment results can are satisfactory, its effectiveness increases and the complication rate decreases.

Keywords: Therapeutic plasma exchange, neurological disease, pediatrics

INTRODUCTION

Therapeutic plasma exchange (TPE) is a treatment method applied to eliminate pathogenic material or components that occur due to a disease and cause morbidity. It is applied to various neurological, hematological, renal and autoimmune diseases. The effectiveness of TPE is associated with the patient's changing plasma volume, the distribution of pathogenic material, and the rate of synthesis. The standard indications have been determined by the American Apheresis Association (ASFA) and are advisory and non-binding.[1] Autoimmune neurological diseases seen mainly in children; Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM) and autoimmune encephalitis.

GBS is an acute, usually symmetrical and typically ascending paralysis disease caused by inflammation of peripheral nerves. Intravenous immunoglobulin (IVIG) is the first choice for treating pediatric patients. Plasma exchange is applied to eliminate

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circulating antibodies or other responsible factors.[2] Early (first 7 days) plasmapheresis significantly reduces morbidity (ASFA category I, grade 1A).

Acute disseminated encephalomyelitis is an inflammatory demyelinating disease of the central nervous system that affects children and young adults. Steroids are the main treatment option. In the absence of adequate response, treatment can be supported with IVIG and plasmapheresis (ASFA category II, grade 2C).[3]

The clinical manifestations of autoimmune encephalitis consist of a wide spectrum, such as seizures, movement disorders, behavioral and mood changes, psychosis, cognitive impairment, and autonomic dysfunction. The treatment includes steroids, IVIG and plasma exchange as first-line therapy (ASFA category I, grade 1C).[4]

This study was conducted to determine the indications, efficacy, safety and complications of TPE in pediatric autoimmune neurological diseases.

MATERIALS AND METHODS

A total of 20 children, 11 (55%) girls and 9 (45%) boys, who were hospitalized in the pediatric intensive care unit (PICU) between January 2017 and December 2021 and underwent TPE due to neurological diseases, were included in the study. IVIG was administered as the first treatment in all the patients, and steroid treatment was also applied in 60% of the patients. Plasma exchange was applied to patients whose clinical and laboratory parameters did not improve.

Plasma exchange was performed at the bedside with a PrismaFlex© (Gambro, Lund, Sweden) device. Fresh frozen plasma (FFP) was preferred as the replacement fluid (19 patients, 95%), and 5% human albumin was used in patients who had an allergic reaction to plasma (1 patient, 5%). It was aimed to replace 1-1.5 times the estimated plasma volume calculated. The formula 70 x weight (kg) x (1-Hct) was used for the estimated plasma volume. Anticoagulation was achieved with citrate or heparin, depending on the clinical condition of each patient. This study was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 08.10.2020/323).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) 21 package program. Normality was evaluated with Shapiro-Wilk tests and histogram plots. Data were expressed as mean, minimum, maximum, frequency, and percentage.

RESULTS

The ages of the patients ranged from 6 to 237 months, with a mean age of 63.16±183.12 months. Neurological TPE indications of the patients were autoimmune encephalitis (50%, n=10) GBS (45%, n=9) and Acute Demyelinating Encephalomyelitis (6.7%, n=1), respectively. An average of 4 sessions of TPE (minimum 2, maximum 9 sessions) was applied to the patients. 45% of the patients were followed up with invasive mechanical ventilation and 15% with non-invasive mechanical ventilation. TPE was performed by inserting a double lumen central venous temporary hemodialysis catheter. The internal jugular vein (60%, n=12), femoral vein (35%, n=7) and subclavian vein (5%, n=1) were used for venous access, respectively.

The mean Pediatric Risk of Mortality Score III (PRISM III) score of the patients was calculated as 16.95±9.90. The clinical and demographic data of the patients are summarized in Table 1.

Unfractionated heparin was used mostly in anticoagulant treatment (90%, n=18). The Citrate was preferred (10%, n=2) in patients who underwent TPE with continuous renal replacement therapy. Catheter occlusion was observed in 2 (10%) patients, allergic reaction in 1 (5%) patient, and hypotension in 1 (5%) patient as complications of TPE.

Muscle strength of patients with GBS was evaluated according to the Medical Research Council scale[5] before transfer to the service. It was determined that the score increased from 0 to 1 in two patients, from 0 to 3 in three patients, and from 1 to 5 in four patients. While acute phase reactants regressed and neurological evaluation improved in 9 of the patients diagnosed with encephalitis, one patient died from septic shock. One patient

Table 1. Clinical and demographic data of the patients

		Min.-Max.	Mean ± SD
Age (mounts)		6-237	63.16±183.12
PRISM III score		0-40	16.95±9.90
Total number of sessions		2-9	4.66±2.61
Days in PICU		2-109	23.61±20.45
		n (15)	%
Gender	Female	11	55%
	Male	9	45%
Mechanic ventilaion (MV)	None	8	40%
	IMV*	9	45%
	NIMV**	3	15%
Neurological disease			ASFA indication
Autoimmune encephalitis	10 (50%)		I/1C
Guillain-Barre syndrome	9 (45%)		I/1A
Acute demyelinating encephalomyelitis	1 (5%)		II/2C

*IMV: Invasive mechanical ventilation, **NIMV: Non-invasive mechanical ventilation, Min.: Minimum, Max.: Maximum, SD: Standard deviation, ASFA: American apheresis association, PICU: Pediatric Intensive Care Unit

was transferred by tracheotomy and the other patients were transferred by spontaneous breathing. The mortality rate was 5% in neurological patients who underwent TPE.

DISCUSSION

TPE is successfully applied in various pediatric neuroimmunological diseases, often acute and chronic inflammatory polyneuropathy, acquired demyelinating diseases of the central nervous system, autoimmune encephalitis, paraneoplastic syndromes, and inflammatory vascular diseases of the central nervous system.[6-10]

Özkale et al.[11] reported that the most common indication in 22 pediatric patients who underwent 135 sessions of TPE was inflammatory neuropathy, followed by acquired demyelinating disease, autoimmune encephalitis, and paraneoplastic limbic encephalitis, respectively. In a study published in 2019, in which 58 pediatric patients who underwent TPE due for neurological diseases were evaluated retrospectively, it was reported that 36% of the patients were treated with category I, 27% with category II and 12% with category III according to ASFA criteria (11th). It was stated that before the TPE application, 90% of the patients were given anti-inflammatory/immunomodulator treatments consisting of steroids and 78% IVIG treatment, and the average time between the onset of the disease and the application of TPE was 25.5 days.[12] In our study, TPE was applied to 10 patients with a diagnosis of autoimmune encephalitis, 9 patients with a diagnosis of GBS, and 1 patient with a diagnosis of ADEM. Of these patients, 19 were in the ASFA I category and 1 in the ASFA II category. Two of the patients diagnosed with autoimmune encephalitis had received IVIG, 2 steroids, and 6 IVIG + steroids treatment before TPE application.

Previous studies have showed that response rates with TPE in autoimmune encephalitis range from 47% to 85%.[11,12] All the 5 patients treated with TPE in this study showed mild improvement with a median one point improvement in mRS score. IVIG had been administered before TPE in all patients with autoimmune encephalitis, and indications were dominated by intractable epileptic seizures. Moreover, previous studies have demonstrated that time to TPE seems to be one of the most critical factors for a sufficient response.[13,14]

It has been reported that patients with peripheral nervous system disease respond better to TPE treatment than those with central nervous system disease. Savransky et al.[15] reported that in their study involving 65 pediatric patients who underwent TPE, they observed significant neurological improvement at the end of TPE in 72% of the cases and at 6-month follow-up in 88.5% of them. The authors reported that they did not detect a relationship between the onset of TPE and clinical improvement, unlike studies suggesting that early TPE application within the first 15 days after the onset of the neurological attack is a predictor of 6-month recovery. We also observed that a significant neurological improvement was achieved in the muscle strength evaluation of our patients.

Yıldırım et al.[16] reported in 2021 that; TPE was found to be more effective on GBS, autoimmune encephalitis and myasthenia gravis, less effective on ADEM and febrile infection-related epilepsy syndrome. There was no correlation between improvement with TPE and clinical parameters, including age, sex, diagnosis, disease duration before TPE, presence of intubation, and length of stay in the intensive care unit and hospital.[16]

CONCLUSION

When TPE is applied with appropriate indications by an experienced team in pediatric neurological diseases, treatment results can be satisfactory, its effectiveness increases and the complication rate decrease.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 08.10.2020/323).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.A., S.E., Design: G.A., S.E., H.İ., Data Collection or Processing: H.Y., H.C.T., H.İ., Analysis or Interpretation: H.Y., H.C.T., B.K., Literature Search: G.A., S.E., H.C.T., H.İ., B.K., Writing: G.A., S.E., B.K.

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Case Report

Angioedema Related to Infectious Mononucleosis

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ABSTRACT

Epstein-Barr virus (EBV), a member of the Herpes-viridae family, is a microorganism could be present in various clinical presentations, from upper respiratory tract infection findings to asymptomatic liver function test elevation, from facial paralysis to angioedema. This case report has been prepared to emphasize EBV infection as a rare factor in the etiology of angioedema.

Keywords: Angioedema, Epstein-Barr virus, infectious mononucleosis

INTRODUCTION

Epstein-Barr virus (EBV) infection is common in children, primary EBV infection is usually asymptomatic at young ages, and presents with very different findings as age progresses. Infectious Mononucleosis, an acute infection caused by EBV, presents with very different clinical symptoms.[1] Angioedema is a reversible, localized swelling of the deep cutaneous layers caused by mediators that increase vascular permeability. It is usually non-dependent, asymmetrical, and nonpruritic. It affects the loose connective tissues of the tongue, lips, face, mouth, throat and extremities. It is often a self-limiting, benign condition but may present as a medical emergency due to upper airway obstruction.[2,3] EBV is a rare factor in the etiology of angioedema, but it should be considered in cases that do not respond to conventional anti-inflammatory therapy.

Patient and Observation

A 16-year-old female patient presented with previous medical swelling in both eyes. It was learned that the patient with symptoms of sore throat and high fever for ten days (Figure 1-3). The patient presented to the emergency department on the second day of angioedema findings; with a history of parental dexametasone and pheniramine maleate administration in emergency department and oral cetirizine prescription as maintenance treatment two days ago. It was stated that the angioedema findings of the case did not regress with treatment.

On physical examination, her general condition was good, she was conscious, and her vital signs (body temperature 36.8 °C, heart rate 88/min, respiratory rate 20/min) were normal for her age. In the systemic physical examination of the patient, there was bilateral bufissure edema. In the oropharynx examination, tonsillar hypertrophic, membranous lesions on bilateral tonsils were observed. A few mobile multiple lymphadenopathies smaller than 1 cm in the bilateral cervical chain, measuring 1 cm in the right preauricular, 1 cm in the right submandibular, and 1.5 cm in the left submandibular, were detected. Other physical examination findings were normal. There was no hepatosplenomegaly.

In her history, it was determined that she was being followed up for allergic asthma. There were no additional features in her family history. In laboratory examinations, hemoglobin 14.8 gr/

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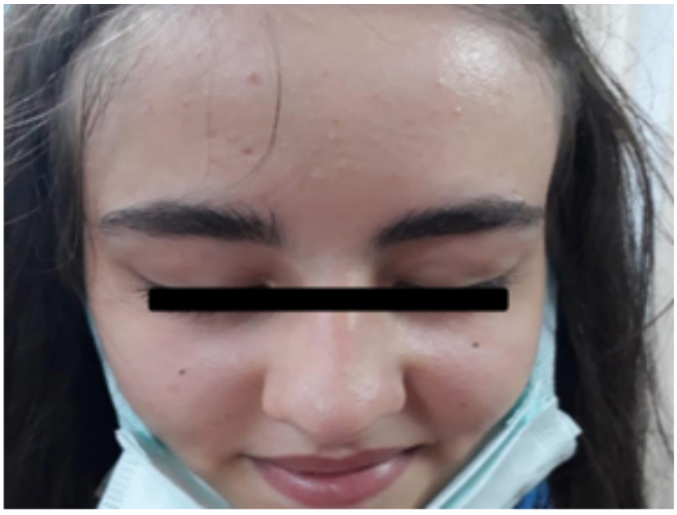

Figure 1. The patient has angioedema on both eyelids

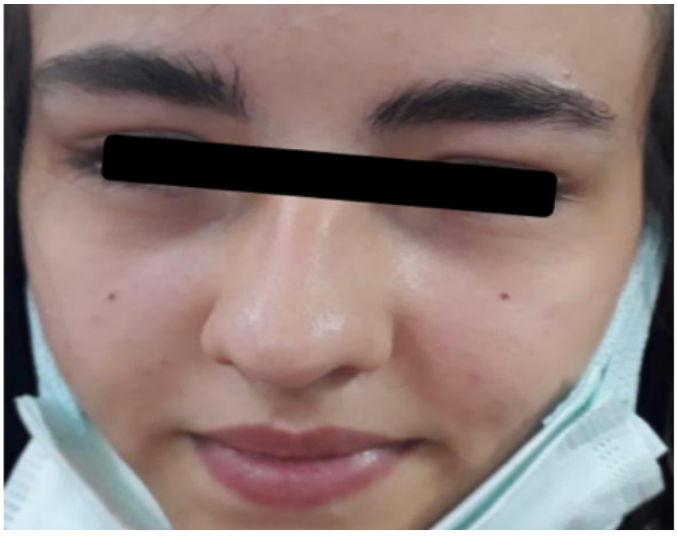

Figure 2. The patient has angioedema under both eyes

Figure 3. The patient has angioedema on both upper and lower eyelids

dL, leukocytes 17800/mm^3, and 61.7% lymphocyte dominance, absolute lymphocyte count 10990, platelet 376000, aspartate aminotransferase (AST) 120 U/L, alanine aminotransferase (ALT) 157 U/L, urea 22 mg/dL, creatinine 0.59 mg/dL. Sedimentation dL, sedimentation 9 mm/hour, autoimmune panel negative. In the viral serology was, EBV viral capsid antigen antibody (VCA) IgM IgM, EBV early antigen and VCA IgG were positive. A Downey cells were observed in the peripheral smear. No abnormality was found in the patient's complete urinalysis.

Considering the current history, clinical, physical examination and laboratory findings, infectious mononucleosis infection and EBV-associated angioedema were considered in the patient. The outpatient follow-up was performed with supportive treatment. In the follow-up of liver function tests, AST 21 U/L and ALT 19 U/L decreased to the normal range.

DISCUSSION

Infectious mononucleosis is a clinical picture in which EBV is seen in 60-70% of childhood age groups in many countries caused by seropositivity.[4] The most common symptoms in patients with infectious mononucleosis are sore throat, exudative tonsillitis, and fever lasting longer than 5 days.[1,5] Lymphomonocytosis is most common in the laboratory. The detection of Downey cells (larger than mature lymphocytes, blue cytoplasm, large, adherent around erythrocytes) in the peripheral smear is helpful in the diagnosis. In many tests used for the diagnosis of EMN, viral capsid antibodies called EBV-VCA, which are formed against the antigens on the surface of the EBV, are detected.[6] The most common complication of the disease was determined as a hematological complication.[7]

Our patient had angioedema, which is a rare complication of EBV. Although cases of urticaria and angioedema secondary to the infection caused by EBV have been reported in the literature, there is no single case of directly related angioedema. Csuka et al.[8], dealing with 107 series of hereditary angioedema follow-up cases, investigated EBNA-1 IGG levels in patients with bradykinin pathway angioedema caused by the immune system triggering of EBV infection and found a strong correlation between them. Nguyen and Christiansen[9] emphasized that periorbital swelling due to EBV infection should not be confused with angioedema in a 19-year-old case and emphasized that angioedema is seen as a rare complication in EBV infection. However, there are many publications in the literature showing that EBV infection in children is associated with cold urticaria.[10]

Angioedema is localized swelling of the skin and submucosal tissues and is usually benign and self-limited. However, in cases of angioedema involving the upper airway, airway obstruction can be life-threatening. Regardless of the underlying etiology, airway protection is critical and life-saving in patients with angioedema.[11] In this study, there was a clinical judge with orbital angioedema secondary to EBV infection, unresponsive to antihistamine treatment and without urticaria.

Ethics

Informed Consent: Parents of the patient provided informed consent to publish the report.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept design: D.L.D., H.Y., S.T., Ö.Y., Data Collection or Processing: D.L.D., H.Y., S.T., Ö.Y., Analysis or Interpretation: D.L.D., H.Y., S.T., Ö.Y., Literature Search: D.L.D., H.Y., S.T., Ö.Y., Writing: D.L.D., H.Y., S.T., Ö.Y.

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Case Report

Lercanidipine Intoxication in A 16-Year-Old Adolescent

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ABSTRACT

Lercanidipine is a 1,4-dihydropyridine calcium channel blocker. For severe toxicity, treatment modalities are based on a restricted range of evidence and clinical experience. This case report describes our clinical experience regarding the treatment of Lercanidipine overdose in a 16-year-old girl. To the best of our knowledge, this is the first reported pediatric case overdose of lercanidipine.

Keywords: Lercanidipine, intoxication, child, treatment

INTRODUCTION

Calcium channel blockers (CCBs) are medications that inhibit the L-type calcium channels involved in myocardial and vascular smooth muscle contractility.[1] They are divided into two groups, dihydropyridine, and non-dihydropyridine, depending on their physiological effects.

Lercanidipine is a 1,4-dihydropyridine CCB.[2] Its selectivity for vascular smooth muscle is more significant than for cardiac smooth muscle.[2] It does not induce sympathetic activation or reflex tachycardia at therapeutic doses and exhibits no negative inotropic effects.[3] However, overdose leads to arterial vasodilation and reflex tachycardia. Additionally, peripheral selectivity is eliminated at severe toxic doses and can affect the myocardium, resulting in arrhythmias, bradycardia, and negative inotropy.[1,4] The time required for an overdose of Lercanidipine to achieve peak effects to wear off is more significant than that for other CCBs.[2]

Data concerning severe toxicity treatment are primarily derived from case series and animal studies. Treatment is therefore based on a restricted range of evidence and clinical experience.

This case report is presented to describe our clinical experience regarding treating Lercanidipine overdose in a 16-year-old girl. To the best of our knowledge, this is the first pediatric case report of an overdose involving the dihydropyridine CCB Lercanidipine.

CASE REPORT

A 16-year-old girl was brought to the pediatric emergency department due to vertigo approximately 2 h after ingestion of the suicide of 30-Lercadip 10 mg tablets used by her mother. At presentation, her Glasgow coma scale was 15, respiratory rate 16/min, heart rate 136/min, blood pressure 80/44 mmHg, capillary filling time <3 s, and SpO_2 100%.

Initial blood gas, fingertip glucose, and laboratory parameters were regular. Sinus tachycardia was present at the electrocardiogram (ECG). Her body weight was 50 kg (-1.35 SDS).

Activated charcoal (1 g/kg) was administered a nasogastric tube two hours after ingestion.

Because of the presence of hypotension and tachycardia at presentation, 0.9% sodium chloride was administered twice at 20 mL/kg. Despite fluid administration for 15 min, her blood pressure remained low (60/30 mmHg), and 10 mL 10% calcium gluconate was administered by intravenous (IV) infusion over 15 min. However, the hypotension persisted, and norepinephrine

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was issued at a starting dose of 0.1 mcg/kg/min and titrated to 0.3 mcg/kg/min. The patient was transferred to the pediatric intensive care unit (PICU).

Following central venous catheter placement in the PICU, insulin therapy at a dose of 0.5 IU/kg/h (hyperinsulinemic euglycemia), glucose infusion (100 mL/h of 10% dextrose), and potassium for preventing hypokalemia were initiated. One hour after hyperinsulinemic-euglycemic therapy (HIET), low ionized calcium levels were reported, and calcium gluconate infusion was started at 0.5 mL/kg/h and raised to 0,7 mL/kg/h. Epinephrine infusion at 0.1 mcg/kg/min was added to the treatment due to the persistence of hypotension. The vasoactive inotrope score was 28.[5] Serial EKGs were taken with serum glucose, calcium, and potassium measurements once every 2 h to prevent clinically significant hypoglycemia, hypercalcemia, and hypokalemia. These serial ECGs were normal apart from sinus tachycardia. No cardiac conduction disorders were observed. The calcium gluconate infusion was stopped on the 4th h due to the development of hypercalcemia. Adrenaline was administered for 20 h, and noradrenaline for 22 h. HIET was maintained for a further 7 h after discontinuation of inotrope therapy and was then tapered down and stopped. Treatments administered during hospitalization plotted with hemodynamic parameters are shown in Figure 1.

The patient was transferred to the pediatric ward 36 h after the presentation. She was finally discharged three days after admission following a psychiatric evaluation.

Informed consent was obtained from the parents of the patient.

DISCUSSION

CCB-related intoxication is associated with significant morbidity and mortality. Therefore, prompt treatment, plays a vital role in patient outcomes. The characteristic features of such intoxication include hypotension, bradycardia, and cardiogenic shock.

The management of CCB overdoses may involve administrating IV fluids, activated charcoal, IV calcium and/or or IV glucagon, IV high-dose insulin, IV lipid emulsion therapy, and IV vasopressor support. However, no set therapeutic algorithm exists for.[6]

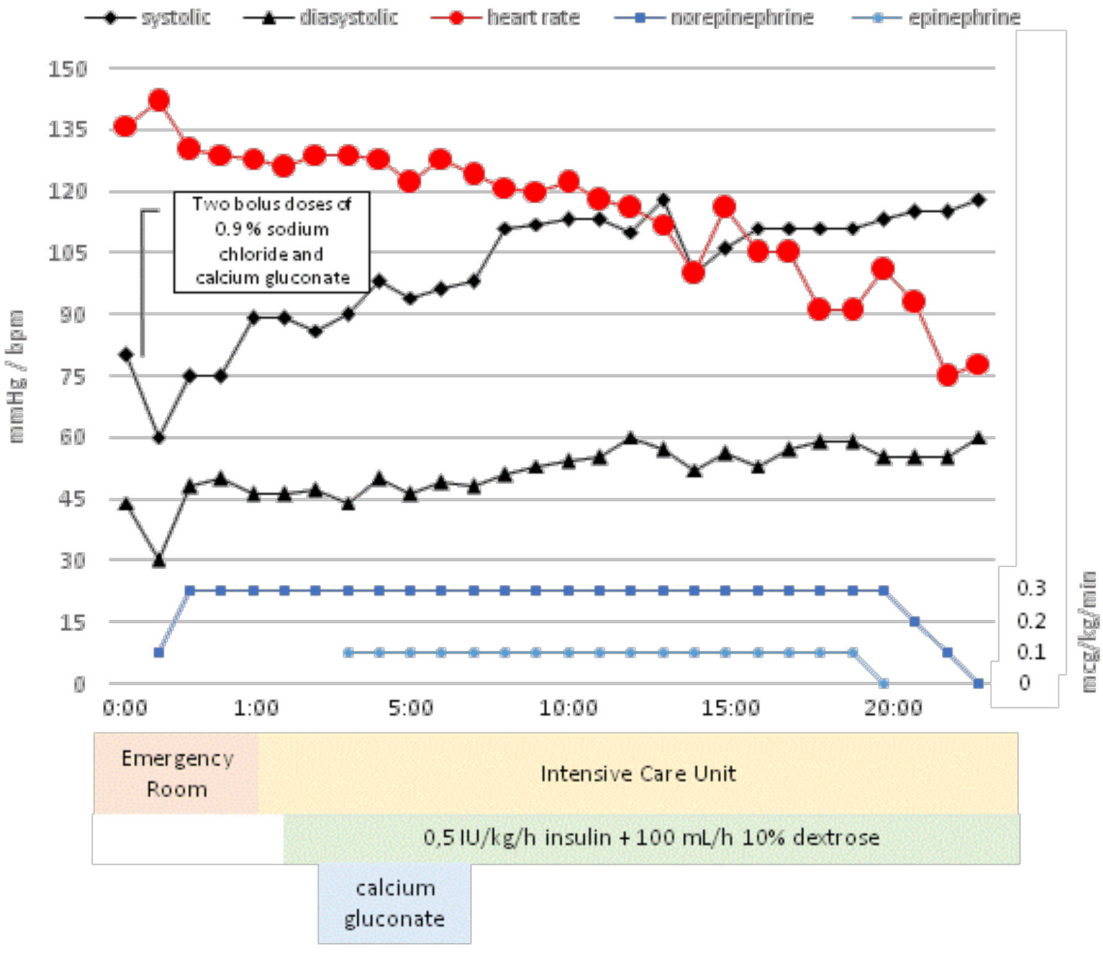

Figure 1. Treatments administered during hospitalization plotted with hemodynamic parameters

In this case, various treatments were required to establish tension stability. However, none of the therapeutic options appear superior to the others. The treatments applied are therefore discussed on the basis of the existing literature.

Activated charcoal[7] was administered since presentation occurred within the first 2 h after drug ingestion. IV fluids represent the initial treatment of hypotension. Our patient received a crystalloid fluid bolus, as recommended, for initial treatment. Since the crystalloid was ineffective, calcium gluconate was initiated to overcome the cardiovascular effects. However, hypotension persisted after calcium administration. Although there have been reports of hemodynamics improving the following glucagon administration[8], this was not applied in this case because glucagon's usefulness in overdose CCBs is doubtful and bradycardia was not observed.

Because of its powerful vasoconstrictive (alpha-adrenergic) effect, norepinephrine was started as the initial vasopressor. Infusion started at 0.1 mcg/kg/min but was titrated to 0.3 mcg/kg/min within 10 min to achieve a mean arterial pressure of 65 mmHg. High-dose insulin therapy was initiated due to the persistence of hypotension (mean arterial pressure 65 mmHg). This therapy exhibits positive inotropic effects in patients with CCB toxicity. Although the mechanism of HIET is not fully understood, its effectiveness and safety have been described in animal models, and case reports.[9-12] HIET was first described in humans in 1999 and improves circulatory shock in four instances of CCB overdose patients when applied as a combination of calcium, glucagon, and epinephrine therapy.[13] Another case study reported rapid hemodynamic stabilization with HIET.[14]

IV calcium gluconate infusion was initiated because of a low ionized calcium value and was maintained until clinically significant treatment-related hypercalcemia was observed. Adrenaline at 0.1 mcg/kg/min was created after 30 min for circulation support.

The options of methylene blue,[15,16] lipid emulsion,[17] and continuous venovenous hemodiafiltration and concomitant charcoal hemoperfusion[18] are available for treating hypotension secondary to CCB overdose refractory to multiple vasopressors and HIETs.

However, these were not employed in this case since the patient tension gradually increased, and her hemodynamic status was stable.

CONCLUSION

This is the first pediatric case of hypotension and reflex tachycardia developing following Lercanidipine overdose and recovery after a series of recommended early treatments.

Although Lercanidipine is safe at therapeutic doses, overdose can result in differing and even fatal effects. We, therefore, believe that early administration will be helpful in the knowledge of the drug's effect mechanism and all the therapeutic options.

Ethics

Informed Consent: Informed consent was obtained from the parents of the patient.

Peer-reviewed: Externally peer-reviewed.

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