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(RESEARCH ARTICLE)

Effect of *Moringa* supplementation in the management of moderate malnutrition in children under 5 receiving ready-to-use supplementary foods in Niger: A randomized clinical trial

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Abstract

Each year in Niger, more than 40% of children under 5 years suffer from chronic malnutrition and more than 10% from acute malnutrition. The national nutrition rehabilitation protocol encourages the use of local foods. The objective of this work is to analyze the impact of supplementation in *Moringa oleifera.* We conducted a randomized double-blind clinical trial in 400 children with moderate acute malnutrition (MAM) aged 6 to 59 months admitted to outpatient nutritional recovery centers (CRENAM). The children were divided into two groups; one group received Ready-to-Use Supplemental Foods (RUSF) and dry leaf powder from *Moringa oleifera* and the other group received RUSF and placebo. We did not find any difference on average weight gain between the two groups or on mid-upper arm circumference and size. The median length of stay in CRENAM was 5 and 4 weeks for *Moringa* and placebo respectively, with no statistical difference (P=0.522). The cure rate was 82% (2.72) in the *Moringa* group with a RR of 1.03 (0.94 to 1.13) slightly in favor of *Moringa*. Renal and hepatic toxicity of *Moringa* was not observed. From this clinical trial, it could be held that *Moringa* supplementation, despite the presence of nutritional indices in favor of *Moringa*, does not have a significant effect on the nutritional recovery of MAM children but that *Moringa* has no renal or hepatic toxicity. Supplementation in subjects already on dietetic treatment, dose reduced to minimum and duration of supplementation seems to have played a role in this absence of effect of *Moringa*.

Keywords: *Moringa oleifera*; Powder; Malnutrition; Supplementation

1. Introduction

Niger, a landlocked Sahelian country, is repeatedly confronted with serious food and nutrition crisis, the main victims are children under five (5) years of age, subjects of acute and chronic malnutrition. The National Institute of Statistics (INS) Survey on Vulnerability to Food Insecurity in 2013 found that 3.5 million people were severely or moderately

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food insecure, whether 20% of the total population. At the same time, more than 7.5 million people, whether 43% of the population, were classified as "at risk", that is to say, in a state of fragile food security [1]. According to the results of nutritional surveys published from 1992 to 2014 [1-11], the vulnerable groups mentioned above still had a nutritional status of concern. The prevalence of chronic malnutrition (CM) exceeds the critical threshold of 40% and that of global acute malnutrition (GAM) exceeds 10% every year, despite the many efforts made by the Nigerian Government and its partners. Since the 2005 food and nutrition crisis, Niger has developed and implemented a National Acute Malnutrition Management Protocol (NAMP), which was revised in 2012 to make the fight against malnutrition more effective. With 898 centers for nutritional and medical recovery from severe acute malnutrition (SAM) and 1145 centers for moderate acute malnutrition (MAM), Niger has one of the largest programs for the management of acute malnutrition (AM) in West Africa [12]. In 2016, malnutrition prevention strategies were defined and integrated into the NAMP; it is essentially the promotion of good nutrition practices [13]. These strategies strongly recommend the use of recipes based on local products enriched with multi-micronutrients including fruits and vegetables in the prevention of malnutrition and nutritional recovery of AM. Local solutions may exist with regard to the availability of certain local foods whose use could be a means of preventing malnutrition and even of managing malnutrition. Among these foods, we have identified Moringa *oleifera* to whom the literature attributes a very interesting composition for human nutrition [14,15]. Moringa is a leafy vegetable, grown in many countries including India, Nigeria, Senegal, Ethiopia, Niger where it is widespread and available for 50 to 60 years [15]. Traditionally consumed in these countries, Moringa is now used in some malnutrition programs, particularly in Senegal, India, Benin and Zimbabwe [15] but the evidence of its real added value as a safe and effective food supplement is still empirical [15,16]. The literature available on its composition describes it as a nutritious food rich in protein with a digestibility of 56% [17], vitamins and other trace elements but its effectiveness in the prevention and management of malnutrition remains to be documented. We conducted a randomized double-blind clinical trial with the main objective of analysing the effect of Moringa supplementation on the nutritional recovery of children 6 to 59 months of age admitted to outpatient nutritional recovery centers for moderate malnourished (CRENAM), receiving nutritional treatment with RUSF [13], in the Tillabéry and Maradi regions of Niger. The secondary objective was to determine the biotoxicity of Moringa in these children with the following assumptions:

Supplementation with dry *Moringa* leaf powder would improve the healing rate of children treated with RUSF in CRENAM. Since the RUSF diet is considered as a supplement that does not dispense the child from the regular daily diet, usually low in protein and micronutrients in our context, we have estimated that the supplementation of the child's daily menu, with *Moringa* powder would compensate for this poverty of the family food ration. The powder of dry leaves of *Moringa* has in fact a high protein content of the order of 30 to 35% and also mineral salts including calcium, iron, potassium, sodium and magnesium. In addition, *Moringa* is credited with a good content of essential amino acids and vitamins in particular A [14,17]. The digestibility of its protein is 56% [17]. It has been suggested that, given at a dose of 10g per day, Moringa dry leaf powder improves the nutritional status of malnourished children [16,18 ,19]. The coverage of the RNI (Recommended Nutritional Intake) per 10 g of *Moringa* given in supplementation would be 18% for proteins, 52% for calcium, 25% for magnesium, 17% for potassium, 30% for iron, 100% for vitamin A, 9% for vitamin C and 2% for zinc and phosphorus [16,20]. The quantities covered are described in table 3 below. The supplementation with *Moringa* would thus enrich the family dish (considered low-nutrition) that should necessarily be brought to the child even under RUSF as specified in the national protocol. It is from this additional supplemental enrichment that we expected to observe the additional effects of *Moringa* compared to placebo. With the 2.5 g of protein provided by the supplementation of 10 g of *Moringa*, knowing that one gram of protein corresponds to 4 kcal, it is a supplement of 10 kcal that is brought to the child every day. Given that all the additional energies are used by the body for growth and that each 5 kcal makes 1 gram of weight gain, we hoped that this supplementation will lead to weight gain of up to 2 grams per day [21]. As malnutrition is most often associated with iron deficiency anemia, which is a form of malnutrition and a source of slowing down growth, we hoped that the contribution of 5,3 mg of iron per 10 g of *Moringa* would help prevent and/or treat anemia. Zinc deficiency is generally associated with malnutrition with the potential for stunting, we estimated that the intake of 100 µg contained in the 10g of *Moringa* could help reduce the differences in intake and help the child's growth, especially since the body does not have a zinc reserve [21]. Classified as a type I nutrient whose deficiency can result in growth retardation, the contribution of more than 50% of calcium needs by the 10 g of *Moringa* allows us to hope for prevention and/or mitigation of malnutrition [21]. With malnutrition, sodium pump activity is reduced and cell membranes are abnormally permeable, resulting in increased intracellular sodium and decreased intracellular potassium and magnesium [21]. Thus, the intake of potassium and magnesium supplement should help to slow down this process of their loss and compensate for their loss. It is based on the combined effects of all these different micronutrients necessary for enzymatic processes and the use of proteins, lipids and carbohydrates [21] that an improvement in the nutritional status of children supplemented with *Moringa* was expected.

Moringa dry leaf powder is neither hepatotoxic nor nephrotoxic.

2. Methods

2.1. Design of the study

Our study "The Effect of *Moringa* Supplementation in Managing Moderate Malnutrition in Children Under 5 receiving Ready-to-Use Supplementary Foods in Niger" is a randomized, double-blind clinical trial. Neither the one who distributes nor the one who receives the product knew its nature by its physical appearance, color, taste or conditioning. It is a prospective bicentric study with two parallel groups, which in addition to common therapeutic and dietary treatment, had each received a different supplement including a placebo. This treatment was done on an outpatient basis with follow-up every two weeks at CRENAM.

2.2. Ethics

Before children are included in the study, oral consent from mothers was required after explaining the study and its objectives under the sponsorship of the management committee which is the community structure that represents populations at the health centers level and which prior to the launch of the study signed a written consent on behalf of the community through its president. The prior written agreement, dated and signed by the National Advisory Committee on Ethics under number 005/2015/CCNE was obtained before the start of the trial.

2.3. Study Site and Participants

The clinical trial took place in two CRENAM, one in Ouallam and the other in Madarounfa in the Tillabéry and Maradi regions respectively.

These CRENAM are public structures that are an integral part of the Integrated Health Center (IHC) corresponding to the first level of healthcare in the health system in Niger offering the minimum package of activities. They are maintained by a qualified state nurse with at least five (5) years of experience, assisted by other nurses, midwives or social workers. Since the 2005 nutritional crisis, the staff of these *IHC* have been trained to manage the MAM according to the NAMP. It is this protocol that determines the criteria for admission to nutritional recovery centers and the management of MAM based on WHO standards. Thus, the criteria for admission to CRENAM for children aged 6 to 59 months are Weight(W)/Height (H) ≥ - 3 Z-score and < -2 Z-score and the absence of bilateral edema [13]. These criteria, coupled with the oral consent of the parents, were the inclusion criteria for our study. Children admitted to CRENAM reside either in the chief town of the IHC (radius of 0 to 5 km) or in the surrounding villages located from 5 to 15 km from the chief town of the IHC. As a result, there are two types of origins: urban for residents in the capital of the IHC and rural for those who reside beyond the capital. Management of MAM in CRENAM involves dietetic treatment with outpatient RUSF and medical treatment [13]. All children who arrive at CRENAM benefit from clinical and anthropometric examinations on the basis of which they are classified as malnourished or not and the type of malnutrition. When they are classified as moderately malnourished, they are admitted to the CRENAM program. Recruitment is done as the children are admitted to the centers. A total of 1048 children were admitted to CRENAM during the study period. Of these, four hundred (400) were selected for the trial, divided into two groups of two hundred (200) children each following the randomization list. Each center had its own randomization list. Input disruptions in CRENAM sometimes slowed down the progression of recruitment and therefore prolonged the duration of the study. As a result, some 578 children did not start the study and had to be excluded from it because they could not benefit from treatment by breaking inputs when they were diagnosed. They were reoriented to the nearest CRENAM without being included in the study. Additional stocks were sometimes requested from neighboring CRENAM in order to ensure the continuity of the management of the children enrolled for the study.

2.4. The intervention

This clinical trial ran from January 2015 to November 2017. It involved 400 children aged 6 to 59 months for an average age of 17 months. After inclusion, which is based on clinical and anthropometric criteria, the children were randomly assigned to a randomization list between two groups to receive a supplement in the form of dry leaf powder, either placebo or *Moringa* at a rate of 10 g per day per child. Both groups also received equally the treatment of malnutrition with the RUSF according to the national protocol. It is a two-week treatment that was given to each child regardless of the group, as well as the supplement taken by the group. The salad and the *Moringa* were packaged in identical bags, which did not allow them to be differentiated on board as much by their taste as by their physical appearance. The study begins for each child from the day of their admission until their exit from CRENAM which occurs after the assessment of the nutritional status of the child. Follow-up varied from two to 15 weeks depending on the child's response to treatment. The randomization list was developed using Excel software by the primary investigator and provided to the

primary supervisor of each center; These were randomization blocks of 10 patients with 5 in each group. The supplement numbers to be received were assigned to the children by the senior supervisor.

This intervention was preceded by a test of acceptability of Moringa powder. The figure below summarizes the scheme of the intervention [22]:

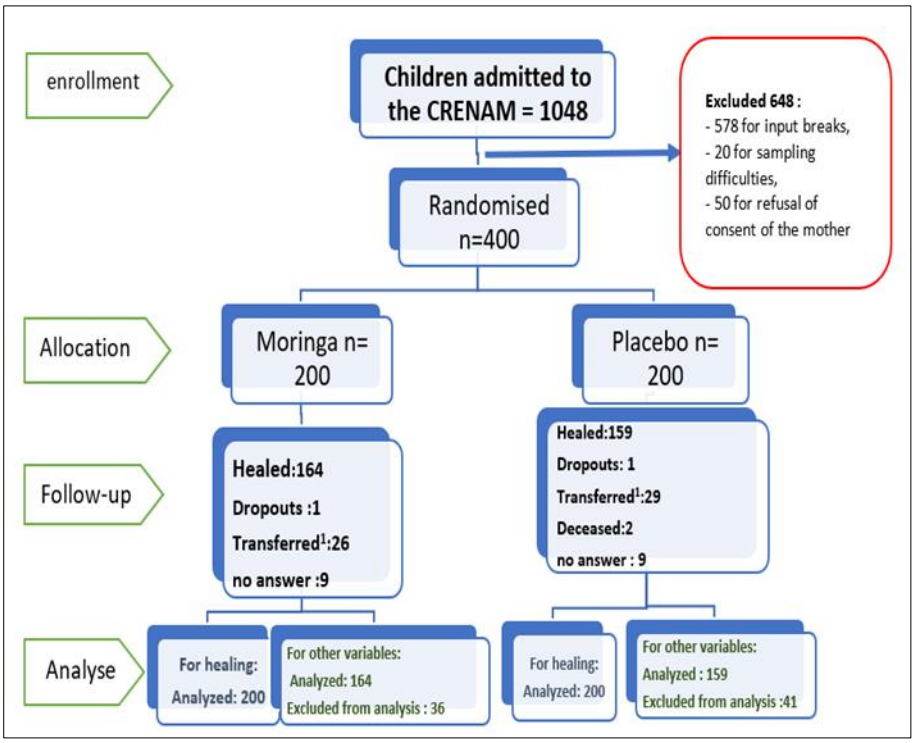

Figure 1 Diagram of the intervention

[1]Transfers are referred to outpatient nutritional recovery centers for severe, uncomplicated malnourishment (CRENAS).

2.4.1. RUSF/Plumpy'Sup

Each child admitted to CRENAM received his food ration made of Plumpy'Sup at a rate of 92 g per day either 14 sachets for two weeks. The nutritional composition per 100 g of Plumpy'Sup is detailed in table 1 [23 ,24]:

Table 1 Nutritional composition of Plumpy'Sup

Component	Content (per 100g)
Energy	537 kcal
Protein	12.1 g
Lipids	35 g
Calcium	630 mg
Phosphate	600 mg
Potassium	100 mg
Magnesium	170 mg
Zinc	12.4 mg
Copper	1.4 mg
Iron	11.2 mg

Iodine	140 ug
Selenium	20 ug
Manganese	1.4 mg
Sodium	< 180 mg
Vitamin A	750 ug
Vitamin D	15 ug
Vitamin E	16.7 mg
Vitamin C	60 mg
Vitamin B1	1 mg
Vitamin B2	2.6 mg
Vitamin B6	2 mg
Vitamin B12	2.7 ug
Vitamin K	27 ug
Biotin	60 ug
Folic acid	448 ug
Pantothenic acid	6.6 mg
Niacine	17.5 mg

Each child in the study received in addition to Plumpy'Sup, a 140 g bag containing either dry *Moringa* leaf powder either placebo. Each bag contained a teaspoon.

2.4.2. Placebo

Dry leaf salad powder was chosen as a placebo given its almost identical physical aspects to Moringa and its almost negligible nutrient content. It was obtained by drying directly in the hot sun either under temperatures near 50°C in order to rid it of the few nutrients it would contain in the fresh state, which makes it possible to assimilate its composition with that of the cooked salad. Table 2 below describes this composition of the salad:

Table 2 Average nutritional equivalent provided per 10 g of salad administered as a daily supplement per child

Components	Average daily quantity administered
Total proteins	0.12 g
Mineral elements	
Fe	-
Zn	0.015 mg
Ca	-
Mg	-
K	-
Na	-
Cu	-
Total phosphorus	-

2.4.3. Moringa

The daily amount that was administered per child was 10 g as recommended [25,26] and already used by other authors [18,26] in a related study. The distributors (treating nurses or nutritional assistants) did not know how to distinguish between Moringa powder and placebo. The nature of the two products named A and B throughout the study, held secret by a non-agent health person who does not work at the health centers, was communicated to us only after the analysis of the results. Each child received their initial two-week ration at the IHC. The Moringa used was produced in Niger and packaged with the help of an agricultural cooperative specializing in the production and sale of dry leaf powder from Moringa. The drying of the leaves of Moringa was done in the shade away from the sun in order to avoid the loss of its nutritional values. Before the start of the intervention, the International Institute for Crop Research of Semi-Arid Tropical Zones (ICRISAT) carried out a chromatographic analysis of dry leaf powder from Moringa. The results showed that dry leaf powder from Moringa grown in Niger is rich in protein, micronutrients and minerals [26]. A physicochemical and bacteriological analysis of Moringa powder and salad samples was also carried out at the National Laboratory of Public Health and Expertise (LANSPEX) to ensure the quality of the products administered. There is an absence of pathogenic germs for children such as E. coli, salmonella and Staphylococci. This composition of Moringa produced in Niger suggests that the 10 g daily supplement provided to the child would correspond to the intakes described in Table 3 below:

Table 3 Average nutritional equivalent provided per 10 g of Moringa administered as a daily supplement per child

Components	**Average daily quantity administered**	**Proportion of ANR covered by Moringa 10g (%) administered to children**
Total proteins	2.5 g	18
Mineral elements		
Fe	5.3 mg	30
Zn	100 µg	2
Ca	150 mg	52
Mg	55 mg	25
K	176 mg	17
Na	28 mg	
Cu	0	0
Total phosphorus	4.5 mg	2

2.5. Criteria for Judgment

The primary criterion of judgment in our clinical trial was the cure rate.

The secondary criteria were:

- Weight gain (g),
- Average weight gain in g per kg per day (g/kg/d),
- Length of stay (days),
- The height gain (cm),
- Gain of brachial perimeter (mm).
- Hepatic toxicity
- Renal toxicity

2.6. Sampling

The calculation of the sample size was done using Stata software version IC 12.1, based on the average over the last five years of the cure rate of CRENAM, main site, which is 59% and an expected rate of 75% [13] which corresponds to the minimum value of a good functioning of CRENAM according to the national protocol outside any intervention, with a power of 80% and an alpha risk of 5%. This resulted in a total of 294 children. To account for drop-outs, the sample was

increased by 15%, bringing the total number of children to be recruited to 338, divided into two groups of 169 each. For convenience, the sample size was increased to two hundred (200) children per group, for a total of four hundred (400) children.

2.7. Product Administration

The distribution of the products (*Moringa* or placebo) was made in the same distribution circuit as that of the other inputs on the basis of numbers previously assigned to children according to the randomization list held by the nurse in charge of the IHC. The mothers administered the amount of supplement received by sprinkling the child's family dish at the child's two main daily meals, which were usually millet-based porridge, millet-based paste with sauce, rice with sauce or cowpea mixed with a little oil.

2.8. Blood Collection

On admission, a blood sample was taken from each child in a dry tube without any additive for the determination of transaminases SGOT (IU/L) and SGPT (IU/L), uremia (mmol/L) and creanemia (µmol/L) to assess renal and hepatic function. The same tests were repeated when the child was healed. The samples were transported to the Niamey National Hospital (HNN) in isothermal boxes containing frozen accumulators. Given the almost permanent shortage of reagents in the HNN laboratory, the selection of blood samples to be examined shall be made randomly by the person in charge of the laboratory when taking out the blood samples to be examined in the laboratory in the batch of samples received as part of the study. Selection bias was thus avoided for laboratory examinations. These examinations were performed using a Cobas c311 analyzer. Test results were categorized into two groups based on whether they were above or below the HNN reference thresholds as described in Table 4 for the biological endpoints for assessing renal and hepatic function:

Table 4 Biological parameters

Variables	Threshold (Abnormal values above threshold)
SGOT (UI/L)	> 25
TPMS (UI/L)	>40
Urea (mmol/l)	>4.5
Creanemia (µmol/l)	>80

2.9. Data Collection and Monitoring

Follow-up at CRENAM was done every two weeks as recommended by the NAMP and ends with the child's release from the program. It was provided by the health center team consisting of two to three health workers under the supervision of the nurse-in-charge of the IHC. It consisted of the verification of the nutritional status of the child by the measurement of anthropometric values and the verification of his health status and finally the administration of medical and dietary treatment. At each follow-up visit to CRENAM, it is decided on the outcome of the child which can be either "the continuation of treatment" or "the cured exit" or "transferred". Between the bi-weekly visits, for the purpose of the study, a follow-up at home was provided by women, community relays. They checked compliance with treatment (taking *Moringa* powders or placebo by children by direct observation or according to the mother) by the parents and sensitized them, if necessary, for a good observance of the treatment which involves the consumption of the daily quantity of products by the child. This follow-up was done every day, the first week and then every week thereafter. The relays also checked the child's health and nutritional status. Their presence with the mothers guaranteed the consumption of almost-100% of the doses given to children because they have led mothers to understand that it is a product intended to help treat children and that adherence to treatment must be respected for this purpose. A field supervisor monitored operations under the coordination of the lead investigator.

The data were collected from two data sheets: one by health center officers and the other by community relays. The weight was measured using a Salter model 6SE scale with a maximum capacity of 25 kg and an accuracy of 100g. The mid-upper arm circumference (MUAC) was measured with the tape with an accuracy of 1 mm. The weight and MUAC measurement are done in an undressed child. As for height, it was measured in the child in a lying position for the under 24 months and in a standing position for children aged 24 months and over using a standard roof with a maximum capacity of 120 cm with a precision of 0.2 cm and minimum graduations 0.1 cm. The Z-score weight for child size was determined from the 2006 WHO reference curves [13]. These measures were taken upon admission to enable the child

to be classified as moderately malnourished or not, then on return visits to CRENAM to determine progress and assess nutritional status to decide whether to continue treatment or exit as cured or be transferred to CRENAS.

In addition to anthropometric and biological data, the following data were collected:

Socio-demographic data: child's age (months) from the health log or according the mother answer (less than 24 months vs 24 months or more), sex, mother's education level (educated or not), mother's occupation (housewife or not), household size (number of people living in the household), place of residence (urban or rural), medical history, history of exclusive breastfeeding (exclusively breastfed child up to 6 months), history of malnutrition (child who has had at least one episode of malnutrition before this admission), age of food diversification (age at which a food other than breast milk was introduced into the child's diet).

Clinical data to assess the morbidity of the child at admission and assess the health of the child during the intervention: diarrhea, fever, cough. Diarrhea is defined as the evacuation of at least three soft or liquid stools within 24 hours [27]. Fever is retained if the child has an axillary temperature of 37.5°C or if there is a notion (or antecedent) of a hot body [27]. The cough is retained when the mother reports that her child is coughing. These clinical data are sought at the health center by the nurse on the day of admission and at each follow-up and home visit by the community health worker.

2.10. Statistical methods

The data was first encoded using the Excel software and then imported on the Stata IC 12.1 software from which all the processing and analysis of the data were made. The CRENAM register and the individual form kept by the nurse in charge of the health centers served as sources of verification of the data collected on the survey forms. For each quantitative variable with normal distribution, the arithmetic mean was calculated with its standard deviation (SD) and the median with dispersion measures P25 and P75 for asymmetric distributions. Averages with standard deviations (SD) of the quantitative intake variables were presented along with proportions for the categorical variables. The comparison between the two groups was made using the student t-test for means and the Khi-square test for proportions. For the duration of stay, which concerns only the cured children, the median was calculated and presented with the minimum and maximum values; The Wilcoxon -Mann-Withney test was used to compare the medians between groups. The relative risks of cure and abnormalities of biological parameters and their 95% confidence intervals (IC95%) were calculated. For this purpose, the *Moringa* group was considered to be the exposed group. For anthropometric variables, means (SD) of admission values, gains between admission and exit were presented for each group, as well as differences in means (IC95%) between the two groups and t-test p-value. For biological variables whose distribution was not normal, medians with percentiles 25 and 75 (P25-P75) of admission values and variations between admission and exit were determined within each group. Differences between groups were tested using quantum regressions; the coefficients of the "group" are presented with their IC95%.

3. Results

3.1. Participants (Chart 1)

A total of 400 children, 200 per group, were included in the study because they met the inclusion criteria among the 1,048 who were admitted to CRENAM during the study period. Thus 648 were excluded for: input failure at the time of admission for 578, inability to draw blood for 20 children and refusal of consent of mothers for 50 children.

3.2. Socio-demographic Characteristics

Table 5 provides information on the children's age, nutritional history, home environment and family environment. He demonstrated that randomization produced comparable groups for the key socio-demographic variables of children's age, gender, home environment, history of malnutrition, mother's age and occupation, its parity and household size. For all these variables there is no statistically significant difference between the Moringa group and the placebo group. On the other hand, the age of food diversification is significantly higher in the Moringa group, as is the proportion of educated mothers and the history of exclusive breastfeeding. The proportion of exclusive breastfeeding clearly higher than what is usually found makes us think of an answer bias to the questions.

Table 5 Demographics - Child and Mother Characteristics

Variable	*Moringa*	Placebo	P
Age of children (months)	n=200	n=200	
Mean (DS)	17.8 (8.4)	17.4 (7.5)	0.615
% < 24	83.0	86.5	0.330
Gender	n=200	n=200	
% Boys	47.0	44.5	0.616
History of breastfeeding	n=198	n=200	
Exclusive (%) up to 6 months	77.3	68.5	0.049
Age diversification (months)	n=198	n=196	
Mean (DS)	5.3 (1.5)	4.9 (1.8)	0.017
Residential environment	n=200	n=200	
% Rural	75.5	81.5	0.144
History of Malnutrition (%)	n=200	n=200	
	4.5	3.0	0.430
Mother age (years)	n = 198	n = 198	
Mean (DS)	27.8 (7.0)	28.1 (7.0)	0.670
Parent instruction	n = 199	n = 200	
% who answered yes	22.1	13.5	0.025
Parent occupation (%)	n = 199	n = 200	
Housewife	92.5	96.5	0.077
Parity (number)	n = 199	n = 199	
Mean (DS)	4.5 (2.7)	4.7 (2.7)	0.460
Household size (number)	n = 199	n = 195	
Mean (DS)	10.0 (5.0)	10.2 (5.1)	0.694

3.3. Outcomes of Children

The relative risk (IC95%) of healing (healed vs not healed) is 1.03 (0.94-1.14) in favor of Moringa and the difference (IC95%) between the healing percentages in the two groups is worth 2.5% (-5.2% to +10.2%) (P=0.526).

Table 6 Child Issues

Variables	*Moringa* (n=200)	Placebo (n=200)
% Cured	82.0	79.5
Other issues		
% Transferred to CRENAS	13.0	14.5
% Abandons	0.5	0.5
% Not replying [2]	4.5	4.5
% Deceased	0	1.0

[2] Child who does not respond to treatment beyond 12 weeks.

The length of stay applies only to children who have gone out healed. Thus, the median length of stay is respectively 35 days (7-91) in the Moringa group and 28 days (10-105) in the placebo group (P=0.522).

3.4. Anthropometric Data in Recovered Children

In Table 7, anthropometric data are presented for the healed out-of-home children: weight, height and brachial perimeter, each with its average at admission, the variation at exit for each group, and the difference in variation between the two groups. It was found that the weight gains observed within each group represent respectively 9.4% and 8.4% of the intake weight for Moringa and placebo. There was no significant difference for gains on MUAC and size.

In children 24 months of age or older, the difference in mean weight gain per kg/d between the treated and control groups was 0.69 (-0.55 to +1.93) compared to -0.02 (-0.56 to +0.53) in children under 24 months of age. For the gain in MUAC, a difference between the two groups was also greater among the older age groups, while the difference in size was greater among the younger age groups. However, none of these interactions between age and the treatment group were statistically significant.

Table 7 Anthropometric Data for Recovered Children

Variable	*Moringa* Mean (SD)	Placebo Mean (SD)	Gain Difference (M-P) Mean (CI 95%)	P
Weight (kg)	**n=164**	**n=159**		
admission	7.46 (1.24)	7.12 (1.06)	0.34 (0.09 to 0.59)	0.008
gain (kg)	0.65 (0.33)	0.59 (0.27)	0.06 (-0.00 to 0.13)	0.060
gain (g/kg/d)	3.25 (2.53)	3.15 (1.97)	0.10 (-0.39 to 0.60)	0.682
Size (cm)	**n=162**	**n=158**		
admission	73.85 (6.82)	72.44 (6.16)	1.41 (-0.02 to 2.84)	0.054
gain (cm)	0.55 (0.64)	0.47 (0.61)	0.08 (-0.05 to 0.22)	0.230
MUAC (mm)	**n=163**	**n=154**		
admission	122.06 (4.21)	120.64 (3.65)	1.42 (0.51 to 2.29)	0.002
gain (mm)	5.08 (3.08)	5.58 (2.98)	-0.50 (-1.17 to 0.17)	0.144

3.5. Biological Data

3.5.1. Non-nutritional Biological Data in Healed Discharged Children

Table 8a describes the variations between admission and cure, transaminase, urea and creatinine rates in each of the two groups. There is a decrease in transaminases in the *Moringa* group and an increase in the placebo group. For the other variables, there is little difference between the two groups. The results are similar when considering the % abnormal values (Table 8b); this % decreased for SGOT in the *Moringa* group and increased in the placebo group.

Table 8a Change in median non-nutritional biological endpoints in recovering children

Variables	*Moringa* Median (P25-P75)	Placebo Median (P25-P75)	Difference (IC95%) (M-P) *	P
SGOT Transaminases (UI/L)	**n=53**	**n=33**		
Admission	44 (36 to 63)	39 (31 to 50)	+5 (-5 to +15)	0.322
Difference (E-A) **	-8 (-29 to +3)	+9 (-7 to +29)	-17 (-31 to -3)	0.018
Transaminases TPMS (UI/L)	**n=54**	**n=35**		
Admission	21 (13 to 34)	21 (14 to 32)	0 (-7 to +7)	1,000
Difference (E-A)	-3 (-14 to -11)	+1 (-9 to +9)	-4 (-6 to +8)	0.380
Uremia (mmol/l)	**n=53**	**n=35**		

Admission Difference (E-A)	3.0 (2.0 to 4.1) -0.2 (-1.2 to +0.8)	2.9 (1.9 to 4.3) -0.2 (-1.1 to +0.9)	+0.1(-0.9to+1.1) 0 (-1.0 to +1.0)	0.857 1,000
Creanemia (µmol/l)	**n=52**	**n=32**		
Admission	24 (18 to 29)	23 (19 to 37)	+1 (-4 to +6)	0.678
Difference (E-A)	1 (-8 to +9)	+6 (-5 to +13)	- 5 (-13 to +3)	0.203

M=*Moringa*, P=Placebo; ** E= Exit, A= Admission

Table 8b Change in percentages of abnormal values of non-nutritional biological endpoints in recovering children

Variables	*Moringa* % (n)	Placebo % (n)	RR/Moringa compared to Placebo (IC95%)
SGOT (UI/L) > 25			
Admission	90.6 (48)	78.8 (26)	1.15 (0.94 to 1.40)
Exit	75.5 (40)	87.9 (29)	0.86 (0.70 to 1.0)
SGPT (UI/L) > 40			
Admission	14.8 (8)	5.7 (2)	2.59 (0.58 to 11.50)
Exit	14.8 (8)	8.6 (3)	1.73 (0.49 to 6.07)
Urea (mmol/l) > 4.5			
Admission	17.0 (9)	20.0 (7)	0.85 (0.35- to 2.07)
Exit	18.9 (10)	14.3 (5)	1.32 (0.49 to 3.54)
Creanemia (µmol/l) > 80			
Admission	1.9 (1)	0	-
Exit	0	3.1 (1)	-

3.5.2. Nutritional Biological Data in Healed Discharged Children

Table 9 Change in median nutritional biological endpoints in recovering children

Variables	*Moringa* Median (P25-P75)	Placebo Median (P25-P75)	Difference (IC95%) (M-P) *	P
Hemoglobin (g/dl)	**n=41**	**n=28**		
Admission	10 (9 to 11)	10 (8 to 10)	0 (-4.2 to 6.2)	0.702
Difference (E-A) **	+1 (-4 to 6)	+1 (-5 to 7)	0 (-5.1 to 7.1)	0.743
Iron (µmol /l)	**n= 49**	**n=31**		
Admission	7.6 (6.2 to 9)	8 (5.1 to 10)	-0.4 (-3.3 to 5.3)	0.642
Difference (E-A)	+0.5 (-4 to 4)	+0.2 (-5 to 5)	+0.3 (-5 to 5)	1,000
Albumin (g/l)	**n= 48**	**n=31**		
Admission	41 (37.8 to 44.5)	39.5 (37.6 to 43.5)	+1.5 (-20 to 20.5)	0.984
Difference (E-A)	-0.7 (-18 to 17)	-2 (-24 to 20)	+1.3 (-18.8 to 20.8)	0.883
Blood sugar (mmol/l)	**n= 46**	**n= 24**		
Admission	2.8 (0.9 to 4.0)	1.3 (0.3 to 1.3)	+1.5 (-1.1 to 2.4)	0.481
Difference (E-A)	-0.2 (-1.6 to 1.2)	-0.2 (-1.6 to 1.2)	0 (-0.7 to 1.9)	0.359

Calcemia (mmol/l)	**n= 47**	**n=27**		
Admission	2.3 (2.2 to 2.4)	2.1 (2.0 to 2.2)	+0.2 (-0.9 to 1.3)	0.739
Difference (E-A)	0 (-1 to 1)	0 (-1.3 to 1.4)	0 (-1.4 to 0.7)	0.447
Magnesium (mmol/l)	**n= 48**	**n=27**		
Admission	1.1(1.0 to 1.2)	1.0(0.9 to 1.1)	0.1(-0.4 to 0.6)	0.692
Difference (E-A)	-0.1 (-0.6 to 0.4)	(-0.6 to 0.4)	-0.2(-0.7 to 0.3)	0.397

M= *Moringa*, P=Placebo; ** E= Exit, A= Admission

4. Discussion

4.1. Children's issues

The cure rate in the *Moringa* group was 2.5% higher than in the placebo group but this difference is not statistically significant. However, it exceeded the stated value of the starting hypothesis by 7% (75%); This difference would certainly not be due to supplementation alone as observed also in the placebo group. However, the relative risk of curing 1.03 (CI: 0.94-1.13) in the *Moringa* group compared to the placebo group is weak in favour of *Moringa*. However, with a difference in healing rate of less than 10% between the two groups, there is no statistically significant difference in the improvement of healing in supplemented individuals in *Moringa* as observed by Bidossessi and al. [19] 100% cure in supplemented children in *Moringa* while 2.4% of control children still showed signs of moderate malnutrition, a statistically significant difference. However, in this study of Bidossessi the duration of supplementation was 6 times higher than ours (6 months/ 1 month). In addition to the difference in duration and the limitation of the age range of the beneficiaries to 6-30 months, the study of Bidossessi which also concerned children suffering from MAM used 10 g of powder leaves of *Moringa* per day in one or two taken as a dietary supplement in the absence of any other treatment with RUSF or other dietary food; However, the child should be breastfeeding to be included in the study.

4.2. Anthropometrics aspects

The mean weight gain (MWG) of 3.25 g/kg/day (2.53) observed in the supplemented group in *Moringa* is 0.10 g/kg/day higher than that of children who received placebo, a non-significantly difference in weight gain between admission and exit between the two groups. The weight gain of 9.4% (0.7*100/7.46) that was observed in the *Moringa* group would be superimposed, relatively speaking, on that found by Amivi and al. [28] who found weight gains of 12 to 17.5% with *Moringa* quantities three times higher than ours (30g/day). Amivi and al. [28] who worked on HIV-negative and HIV-positive children aged 6 months to 8 years who each received 30 g of *Moringa* powder per day for 16 weeks without further dietary treatment, found a significant improvement in nutritional status compared to placebo regardless of serological status. In HIV-negative subjects the weight gain is 17,5% for those under one year and 12% for those over one year. This study differs fundamentally from ours on the duration of administration of the product which is four times longer than ours and the daily quantity of the product, three times as large and not associated with any other dietary treatment. Urbain Zongo and al. [18] who used the same dose of 10 g of *Moringa* per day in children 6 to 59 months with an average supplementation time of 5 weeks found a weight gain of 8.9 ± 4.30 g/kg/day compared to 5.7 ± 2.72 g/kg/day in placebo with a statistical significance of the difference. This Zongo study differs from ours in the absence of an associated dietary treatment.

In terms of other outcomes, our study found no differences between the two groups. The two deaths observed in the placebo group occurred at home as a result of malaria access according to the parents. If we consider the difference in weight gain between *Moringa* and placebo which is 0.06 kg or 60 g in total over an average stay of 30 days, we deduce that the supplementation with *Moringa* actually brought an additional gain of 2g (60/30) per day expected from the administration of 10 g of *Moringa* powder either the equivalent of 2.5 g of protein equivalent to 10 Kcal. Therefore, would it have been necessary to administer a greater quantity than the one we administered to obtain a significant difference in the effect of *Moringa*? Proportionally, 7.5 g of protein per day would be expected with the administration of 30 g of *Moringa* powder or 30 Kcal which could generate a weight gain of 6 g per day [21]. The recommended amounts being between 10 and 30g per day [26,27] and that we used only the minimum dose of 10g, a test with a higher dose than the 10g and/or a non-association of other dietary treatment apart from supplementation with *Moringa* may provide more enlightening conclusions. This approach that we suggested should then be spread over a longer duration of supplementation as done by other authors [19, 28].

4.3. Aspects on nutritional biological parameters

The increase in iron between intake and exit 2.5 times higher in the *Moringa* group (+0.5) compared to placebo (+0.2) has been observed but the difference between the two groups is not significant. Hemoglobin levels also increased in both groups, but with no difference between the two. The expected effect through supplementation seen from the angle of iron intake by the *Moringa* being the attenuation of anemia haven't be observed; only the tendency to improve the hemoglobin level (+1g/dl) have been observed without being able to attribute it to *Moringa*. Urbain Zongo and al. [18] also found no significant increase in hemoglobin levels. We did not see an increase in other non-nutritional biological parameters. Amivi and al. [29] who worked with HIV-negative and HIV-positive children aged 12 months to 9 years by administering 30 g of *Moringa* powder per day for 16 weeks, observed a significant increase in serum iron and hemoglobin levels in both groups compared to placebo after 14 weeks of *Moringa*.

4.4. Length of stay

The median length of stay from admission to healing that was 4-5 weeks in both groups was almost identical with no statistically significant difference; almost the same duration observed by Urbain Zongo and al. [18] in a clinical trial of *Moringa* supplementation in children 6-59 months of age. It is also the same length of stay that was observed by Iqbal H. et al. in a randomized double-blind clinical trial involving soy/RUSF supplementation versus milk/RUSF [30]. It remained within the standard allowed by the NAMP, which sets it at less than 8 weeks [13]. The 6-month (24 weeks) duration used by Bidossessi and al. [19] or Amivi et al. [28] for a 16 weeks duration with more conclusive results on the efficacy of *Moringa* provides arguments for extending the duration of supplementation.

4.5. Aspects on bio toxicity

As described by other studies we observe that at intake SGOT and SGPT transaminase rates are high in malnourished children with a higher proportion for SGOT due to liver dysfunctions caused by malnutrition [21,28,30,31]. The higher proportion in our population of 90% compared to 70% found by Félicitée and al. [31] could be explained by the quasi-association of parasitosis with malnutrition among Nigerien children at this age [13] and which alone would constitute causes for the rise of transaminases [21]. At the exit these rates have decreased by 18% of its median value to move towards normalization in children under Moringa. Amivi and al. [28] observed a reduction in transaminase rates of 4 to 9 times higher than placebo. In contrast, among those on placebo, there was an increase of about 23% in the median value. It is as if *Moringa* supplementation helped to initiate the normalization of the SGOT transaminase rate, which was initially high due to malnutrition, while it remained even higher at the end of the program in the placebo group. The variations observed in the *Moringa* group were statistically significant suggesting a hepatoprotective effect by *Moringa* supplementation, as found by AbdulrahmanK and al. in a review of hepatoprotective plants used in Saudi Arabia [32]. This also indirectly denotes the contribution to nutritional recovery induced by *Moringa* supplementation. The difference in variation with the SGPT in favor of *Moringa* was in the same direction and the RR of 1.73 (0.49 to 6.07) comforts it. Both uremia and creanemia remained normal in both groups. Amivi and al. [28] even observed a 20% reduction in the value of creanemia in subjects under *Moringa* compared to the starting value after administration, recall 30g/day of *Moringa* powder for 16 weeks. This finding would suggest the absence of nephrotoxicity of dry *Moringa* leaf powder taken at doses of 10 g per day in children (a maximum dosage of about 2000 mg/kg weight). This lack of toxicity of *Moringa* found in this study confirms that already observed in rats even at extreme doses of 5000 mg/kg weight on all vital functions including renal and hepatic [33,34]. For the rest of the rat studies even histologically established a protective effect of the kidney by *Moringa* [35].

4.6. Limitations

Frequent ruptures of reagents at the laboratory level of the national hospital considerably limited the number of subjects who benefited from the laboratory examinations to be carried out during recruitment and exit from CRENAM. Thus, in relation to the missing data, we only took into consideration the subjects who had benefited from the admission and exit examinations for each type of test.

5. Conclusion

The results of this randomized double-blind clinical trial do not suggest that powdered supplementation of dry leaves of *Moringa* would improve the cure rate in malnourished children even though a slightly healing RR in the *Moringa* group is observed. However, the study found that *Moringa* did not affect renal and hepatic function. The elevated transaminases at the admission of subjects due to malnutrition decreased significantly in subjects under *Moringa* compared to placebo and the urea and creanemia levels remained normal. Serum iron and hemoglobin levels, although increased, were not significantly different from placebo. In total, this study shows that, notwithstanding the presence of nutritional indices in favor of *Moringa*, the complex supplementation with dry leaves powder of *Moringa* did not make

it possible to show any benefit in terms of nutritional recovery but allowed to confirm the absence of renal and hepatic toxicity of *Moringa*. Similar and/or related studies that have established evidence of improved nutritional status, healing and weight gain all differ from our study by not combining any other dietary treatment apart from *Moringa* supplementation. In addition, most of these studies also differ from our study in that the duration of supplementation is 4 to 6 (24 weeks/4 weeks) times higher than ours and the amount of *Moringa* given daily is three times higher (30g/10g). It has therefore become clear to us that any clinical trial that wants to establish the efficacy of supplementation with dry *Moringa* leaf powder should avoid grafting the intervention on an existing dietary treatment and should also spread the supplementation on an average duration of 16 to 24 weeks.

Compliance with ethical standards

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Disclosure of conflict of interest

None of the authors and co-authors had any conflict of interest in this work.

Statement of ethical approval

The clinical trial was carried out after the agreement of the National Ethics Committee through its decision N°005/CCNE dated March 4, 2015.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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