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Comparative efficacy of Antidiarrheal activity of *Mebarid* vs. *Diarex*, Ayurvedic Antidiarrheal formulations in children with acute diarrhea.

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ABSTRACT

In clinical practice, nonspecific anti-diarrheals (allopathic and ayurvedic) are commonly used by clinicians along with routine treatment, to hasten the recovery and to provide psychological relief. Although they are used extensively in clinical practice, there are variable reports regarding their efficacy and utility. This prospective observational study was carried out in two private clinics run by paediatricians to compare the efficacy, safety, and tolerability of *MEBARID* versus *DIAREX*, ayurvedic polyherbal anti-diarrheal formulations in the treatment of acute diarrhea. Children suffering from acute diarrhea (aged 2 y to 10 y) who presented to the clinic with acute diarrhea and fulfilling selection criteria were enrolled and divided into two treatment groups viz, *MEBARID* and *DIAREX*. Data collection was done using predesigned case report forms and questionnaires. Outcome measures used were 1) duration of diarrhea, after initiation of treatment 2) no. of diarrheal stools until recovery 3) time (h) required for improvement in stool consistency. We found significant difference in time needed for improvement in stool consistency between *MEBARID* and *DIAREX* (19.95 h vs. 29 h). Administration of *MEBARID* reduced the stool frequency significantly ($p < 0.01$) compared to *DIAREX*. However, the mean duration of diarrhea was significantly reduced by *DIAREX* **(**42.77 ± 1.48 vs. 54.15 ± 1.53). No serious adverse effects were recorded during the study. Administration of *MEBARID* hastened the recovery of children suffering from acute diarrhea significantly by reducing frequency & improving consistency of stools compared to *DIAREX*. But *DIAREX* significantly reduced the duration of diarrhea compared to *MEBARID*.

Keywords : Acute diarrhea, Mebarid, Diarex, Nonspecific anti-diarrheal, Children

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INTRODUCTION

Acute diarrhea is a major health problem in developing countries like India. It accounts for significant morbidity and mortality in children. [1] It is the second leading killer in India next to pneumonia; causing death of more than 1 million children annually. [2]

It is also a cause of anxiety and economic burden to parents of affected children. In India, it is mostly infectious in origin and the toll of diarrhea is highest, as poverty also adds additional burden, and long-term consequences of the vicious cycle of enteric infections, diarrhea, and malnutrition are inevitable.

Acute diarrhea is defined as history of at least three loose or watery or unformed stools in a minimum period of 24 hours and usually for the duration of less than 7 days.[3] Acute diarrhea in children is very often self-limiting within few days. [4] Antibiotics do not alter the course of the disease and have limited role as most episodes of diarrhea are caused by viruses and enterotoxigenic E.coli.[5,6] However, children are in danger of developing dehydration and complications.

ORS forms mainstay in treatment of diarrhea; [7] but it does not reduce frequency & volume of stools or the duration of diarrhea. Hence, in clinical practice, nonspecific anti-diarrheals (allopathic and ayurvedic) are most commonly used by clinicians along with routine treatment so as to hasten the recovery and to give psychological reassurance to patients / parents.[8, 9, 10]

MEBARID and *DIAREX* are ayurvedic polyherbal anti-diarrheal formulations commonly used in clinical practice by pediatricians. But studies comparing efficacy and safety of these preparations are not available. Hence , this study was designed to compare the efficacy, safety and tolerability of *MEBARID* with *DIAREX* in the treatment of acute diarrhea in children.

Table 1: Composition of *MEBARID*

No.	Ingredients	Quantity (mg
i	*Bael (Aegle marmelos)*	100
ii	*Ajmoda (Ptychotis ajowan)*	100
iii	*Lodhara (Sympolocos racemosa)*	100
iv	*Dadim (Punica granatum)*	100
v	*Badishep (Foeniculum vulgare)*	100
vi	*Daruhalad (Berberia aristata)*	100
vii	*Jaiphal (Myristiac fragrans)*	50
viii	*Sunth (Zingiber offcinale)*	50
ix	*Ativis (Acontium heterophyllum)*	50
x	*Kuda (Holarrhena antidysenterica)*	50
xi	*Sugar*	q.s

DIAREX (Himalaya) is a herbomineral ayurvedic preparation in which herbs are mixed with shankha bhasma and is available in tablet form. *DIAREX*, was tested for efficacy in adults in treatment of diarrhea .[11] Efficacy studies in children are few.

MEBARID (S.G. Phyto Pharma) is a polyherbal preparation, is available in liquid dosage form suitable for children. This study is conducted to compare its efficacy with that of *DIAREX* in children

Table 2. Composition of *DIAREX* Tablet

No.	Ingredients	Quantity (mg)
i	*Kuda (Holarrhena antidysenterica)*	245
ii	*Guduchi (Tinospora cordifolia)*	16
iii	*Bael (Aegle marmelos)*	245
iv	*Dadim (Punica granatum)*	82
v	*Shankh bhasma*	61
vi	*Musta (Cyperus rotundus)*	51

To compare the efficacy, safety, and tolerability of *MEBARID* versus *DIAREX* in the treatment of acute diarrhea in children .

MATERIALS AND METHODS:

Setting:

This was a prospective, observational study done in clinical settings for a period of 24 months. Two private pediatric clinics, run by pediatricians were selected after obtaining their permission. The study protocol was approved by Institutional Ethics Committee of MIMER Medical College, Talegaon, Pune.

Study Population:

Children suffering from acute diarrhea and fulfilling the selection criteria (Table 3) were enrolled in the study. Informed written consent was obtained from parents. They were divided into two treatment groups - *DIAREX* and *MEBARID* at the discretion of the pediatrician. Both groups received conventional treatment plus either *MEBARID* / *DIAREX*.

Table 3 : Selection criteria:

Inclusion Criteria for enrollment was as follows:

1. Age: 2 - 10 years.
2. Acute diarrhea of varied etiology.
3. Duration of diarrhea of less than 2 days.
4. Diarrhea with co - morbidity which is not severe.

Children were excluded from the study based on following criteria:

1. Age < 2 and > 10 years.
2. Severe / Iatrogenic / or bloody diarrhea.

3. Diarrhea with severe dehydration / significant systemic illnesses.
4. Children with severe malnutrition (<50% of expected weight for that age) according to IAP criteria.
5. Children receiving antibiotics, pre / probiotics and / or zinc supplements or any other nonspecific anti-diarrheal drug.

Data collection and data analysis

Patients of acute diarrhea attending the clinic were intervened by the pediatrician first. Case history was recorded followed by general examination and systemic examination. Case records were screened to obtain following baseline data : Age, weight, height, immunization status, history of fever, vomiting, degree of dehydration (mild , moderate or severe) or other symptoms, prior use of any medication, duration of diarrhea, character of stool (watery, mucoid , bloody etc), consistency of stool.

Prescription was analyzed in detail. Administration of concomitant medications such as antipyretics, antiemetics were recorded. Parents of children were informed in detail, the study protocol in simple and lucid language. A questionnaire was provided to parents and they were instructed to fill and record the details of the diarrheal episodes till recovery.

All the information was recorded in a predesigned CRF (Case Report Form) including the details of treatment drugs, which was filled on enrolment day in detail and on follow up days. Follow up was done on 3rd, 5thand 7th day of treatment. In cases of failure to follow up, personal visit was done by investigator. A telephonic check was carried out daily. Any episode of complication, adverse effect or need for unscheduled use of IV fluids was recorded.

Parents were sensitized to report the adverse effects like abdominal pain, abdominal distension, drowsiness, lethargy, vomiting or constipation as early as possible.

Outcome variables

Recovery was defined as

1. Production of two consecutive normal stools.
2. Production of one normal stool followed by 12 hours with no stool production.
3. No stool production for a period of 12 hours.

Efficacy criteria:

The primary efficacy criterion was duration of diarrhea - time between initiation of treatment and production of the final diarrheal stool. [13] Secondary efficacy criteria consisted of :

1) No. of diarrheal stools after initiation of treatment until recovery.

2) Time (h) needed for improvement in stool consistency.[14,15]

Tolerability and safety were evaluated by recording the adverse effects experienced during treatment.

Statistical analysis:

Data obtained are expressed as mean ± SEM. It was analyzed statistically by Student's unpaired "t" test. $P<0.05$ was considered as significant.

RESULTS AND DISCUSSION:

Total 201 children were enrolled, 123 in *MEBARID* group and 78 in *DIAREX* group. Both the groups tolerated the treatment well and continued the medications as advised till the end of treatment. Compliance in our study was good. The base-line parameters are shown in table 4.

Table 4: Base-line parameters of patients on enrolment

Particulars	***MEBARID***	***DIAREX***
Number	123	78
Age (y)	4.43 ± 0.20	7.05 ± 0.19
Sex (M:F)	44:56	51:49
Degree of Dehydration (N)		
No Dehydration	69	31
Mild Dehydration	31	28
Moderate dehydration	23	19
Duration of diarrhea before enrolment (h)	42.24 ± 1.34	40.61 ± 1.70
Frequency of stools / day	5.27 ± 0.17	5.49 ± 0.21
Vomiting (N)	26	9
Fever (N)	11	14

Values are mean ± SEM. There was no significant difference between two groups. Stool analysis was done in 3 patients (2 from *MEBARID* group and 1 from *DIAREX* group) as advised by pediatrician. Stool samples were studied for routine pathogens and there was no significant abnormality.

Table 5: Comparison of efficacy of *MEBARID* and *DIAREX*

Group	***MEBARID* (N=123)**	***DIAREX* (N=78)**
Time (h) needed for improvement in stool consistency.	*19.95 ± 1.04	29 ± 1.32
No.of diarrheal stools until recovery.	*4.37 ± 0.14	5.26 ± 0.27
Duration of diarrhea (h)	54.15 ± 1.53	* 42.77 ± 1.48

Values are mean ± SEM.,* $P < 0.01$

Assessment of efficacy:

There was significant difference in time needed for improvement in stool consistency between *MEBARID* and *DIAREX*. (19.95 h vs. 29 h).

Patients on *MEBARID* passed 4.37 ± 0.14 stools before recovery, while patients on *DIAREX* passed 5.26 ± 0.27 stools. *MEBARID* reduced stool frequency significantly ($p < 0.01$) compared to *DIAREX*.

Whereas the mean duration of diarrhea was less for *DIAREX* group **(**42.77 ± 1.48 vs. 54.15 ± 1.53) (Figure 3). Addition of *DIAREX* to routine treatment of acute diarrhea significantly reduced the duration of diarrhea (Table 5, Figure. 1, 2 & 3).Time (h) required for improvement in stool consistency :

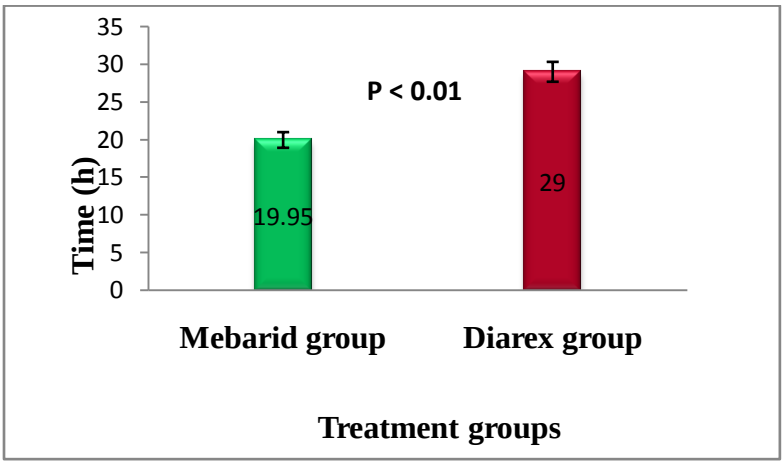

Figure 1. Time (h) required for improvement in stool consistency Bars represent the mean ± SEM.

Stool Frequency: Number of diarrheal stools until recovery

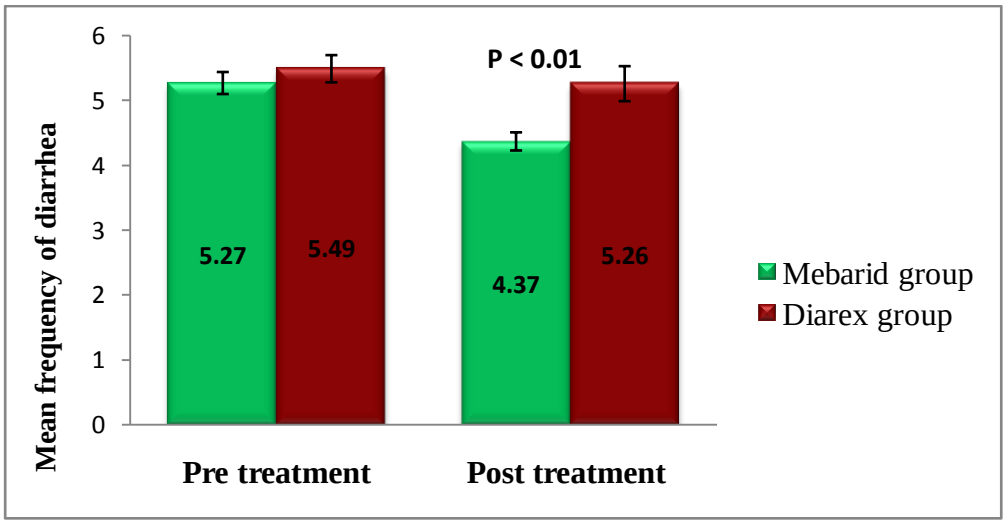

Figure 2. Mean (±SEM) number of stools passed by patients of *MEBARID* group (n=123) and *DIAREX* group (n=78) during the 24 hours before treatment commenced and from the start of treatment until recovery.

Duration of diarrhea:

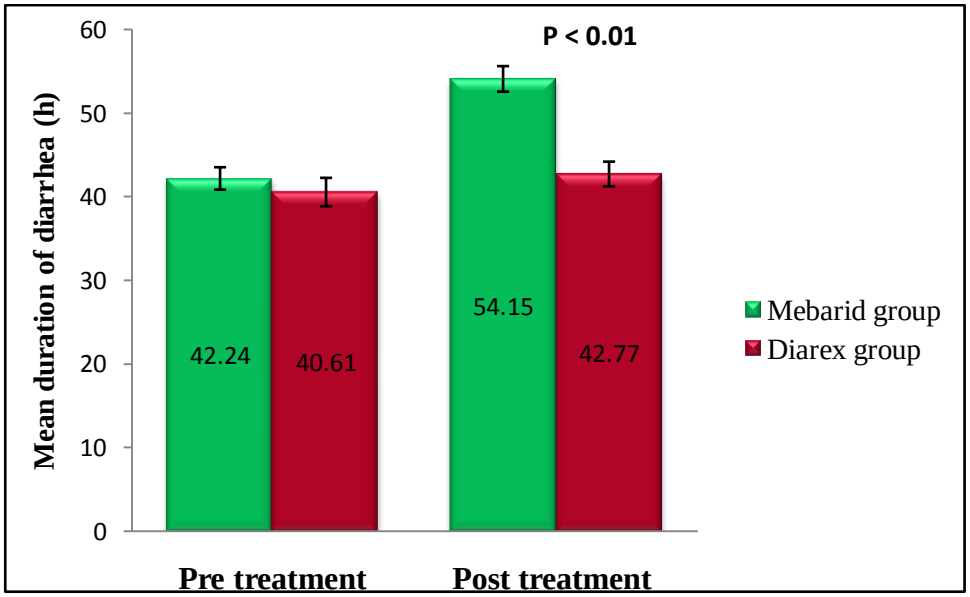

Figure 3. Mean duration of diarrhea before and after treatment in *MEBARID* group(n=123) and *DIAREX* group (n=78). Bars represent the mean ± SEM.

Safety evaluation: Of 201 patients studied, no severe adverse events were observed in children. 7 patients from *MEBARID* group and 5 patients from *DIAREX* group complained of vomiting after initiation of treatment which was relieved by antiemetics. Initially 25 patients had fever on enrolment, which was cured by the second or third day of treatment with antipyretics. (Table 4). 35 patients had vomiting along with diarrhea on enrolment which was cured by day 3 with antiemetics. 9 patients from *MEBARID* group complained of abdominal pain which was relieved by appropriate drugs.

3 patients on *MEBARID* needed admission for IV fluids due to dehydration. No serious adverse effects were recorded during the study.

Present study examined several aspects of *MEBARID* and *DIAREX* supplementation. Stool consistency and frequency, which are primary concerns of the mother are taken care of by both these drugs. *MEBARID* resolved the symptoms of acute diarrhea rapidly and effectively. A decline in the number of loose stools and an increase in solid bowel movements was noted within 24 hrs after the initial visit in *MEBARID* group. *MEBARID* significantly reduced the no. of diarrheal stools and also improved stool consistency earlier compared to *DIAREX*. As is seen that the diarrheal duration was comparable in both groups initially, but after treatment, *DIAREX* supplemented group has shown faster recovery. The duration of diarrhea was significantly shorter with *DIAREX* (42.77 h; $P < 0.01$). Whereas the duration of diarrhea was not altered by addition of *MEBARID* to the routine therapy.

Exact mechanism of action of nonallopathic antidiarrheal agents is not known. However experimental studies have suggested the possible mechanisms.

Phytochemicals such as alkaloids, tannins, flavonoids and terpenes present in active extracts of these preparations are thought to be responsible for antidiarrheal action.

Tannins and flavonoids are thought to be responsible for antidiarrheal activity by intestinal anti-secretory action, and by increasing colonic water and electrolyte reabsorption and also by astringent action. Alkaloids and terpenes are thought to act by inhibiting intestinal motility. [16]

Difference in effectiveness between two drugs could be probably because of presence of 'bhasma' in herbomineral preparation *DIAREX*. Herbomineral preparations are claimed to possess following advantages:1) lack of taste 2) quick action 3) require less dose 4) prolonged shelf life 5) better palatability 6) better patient compliance. [17]

It is claimed that presence of 'bhasma' enhances the absorption and metabolism of herbal ingredients, thus improving efficacy. Nanoparticles present in bhasma are reported to be responsible for fast and targeted action. Bhasma and herbal ingredients are reported to have synergistic action.[18] However, these claims were not confirmed in this study.

The results obtained in the present open label study are preliminary in nature and require further scientific studies with larger sample size. This study did not take into consideration other associated symptoms. Also our study did not take into consideration the socio demographic variables and risk factors like education of parents, socioeconomic status, hygiene, sources of water, overcrowding, nutritional status, immunization status especially of measles, vit A supplementation and rota virus vaccination which may have association with response to treatment.

CONCLUSION:

Addition of *MEBARID* significantly hastens the recovery of children suffering from acute diarrhea by reducing frequency & improving consistency of stools compared to diarex. But *DIAREX* significantly reduces the duration of diarrhea compared to *MEBARID*. Their use may be recommended in addition to routine treatment like ORS.

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