

Original Article

Assessment of Safety and Efficacy of Curkey® Pastille when Administered as a Standalone in Children with Viral Upper Respiratory Tract Infection and as an Adjuvant with Antibiotic Treatment in Bacterial Upper Respiratory Tract Infection : A Randomized, Open-Label Study

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Abstract

Background : Upper Respiratory Tract Infections (URTIs) are caused by a myriad of viruses and bacteria, and commonly affect children. Overuse of antibiotics in children can result in serious side effects. Therefore, it is important to establish a child-friendly formulation that can offer quick and targeted symptomatic relief with minimum side effects. This study evaluated the safety and efficacy of Curkey® pastille (100 mg curcumin) as monotherapy for viral URTI and as an adjuvant with standard care with or without antibiotic therapy in children with bacterial URTI.

Materials and Methods : This was an open-labelled, multi-center, randomized study including 69 children aged 7-12 years. A total of 65 subjects completed the study and were randomized into 3 groups, wherein group A with viral infection received only Curkey® pastille, group B1 (bacterial infection) received only antibiotics, and group B2 (bacterial infection) received Curkey® pastille with antibiotics for 5 days. The outcomes of management after 5±1 day were analyzed in terms of Tonsillopharyngitis Severity Score (TSS), Tonsillopharyngitis Assessment (TPA), Global Assessment of Efficacy and Visual Analogue Scale (VAS).

Results : All three treatments were effective against viral and bacterial infections. The viral sub-group showed significant response within five days of monotherapy with Curkey® pastille. In the bacterial sub-groups, subjects receiving the combination of Curkey® with antibiotics exhibited comparatively quicker improvement of all symptoms than those receiving antibiotics alone. There were no side effects or complications due to Curkey® pastille.

Conclusion : Curkey® pastille effectively alleviated symptoms of viral and bacterial URTIs by delivering active curcumin via buccal mucosal absorption, enhancing the bioavailability of curcumin and making it an excellent adjuvant therapy.

Key words : Curkey® Pastille, URTI, Antibiotics, Curcumin.

Upper Respiratory Tract Infections (URTIs) present as self-limited irritation and swelling of the upper airways with associated cough, runny nose, no signs of pneumonia, or a history of chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or any other condition that would account for the symptoms¹. URTIs are a primary factor in mild morbidity and are frequently seen in both children and adults², and are one of the leading causes of pediatric visits to hospitals. They have an exorbitant cost to

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Editor's Comment :

- The buccal absorption technology of Curkey® pastille (100 mg curcumin) enables optimal absorption of curcumin through buccal cavity into the systemic circulation, leading to enhanced bioavailability.
- It effectively reduces symptoms of viral URTI (when used as monotherapy) and bacterial URTI (when used in combination with antibiotics) among pediatric patients.

society³, Young children are more susceptible to URTIs as their immune systems are developing⁴.

Antibiotics are often prescribed for URTIs due to the risk of secondary bacterial infections and the uncertainty regarding diagnosis⁵. Antibiotics deplete the healthy bacteria in the gut, thus weakening immunity and increasing susceptibility to secondary bacterial infection. Natural antibiotic alternatives can interrupt this cycle⁶. Curcumin is a naturally-occurring active compound extracted from the rhizome of *Curcuma longa*, which has been used in traditional

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Asian medicine based on the range of molecular targets involved in oxidation, bacterial and parasite activity, inflammation, etc⁷⁻¹¹.

Curcumin exhibits antiviral properties by altering the surface protein of viruses, preventing viral entrance and virus budding. Curcumin has rapid metabolism, low intestinal absorption, and lower toxicity at high dosages in humans (up to 12 g/day)¹². When curcumin is administered orally, it undergoes first-pass metabolism before entering systemic circulation at substantially lower concentrations. Curcumin absorption can be improved by administering it through the buccal mucosa. Since curcumin is lipophilic in nature, its principal transport method is passive translocation through the buccal mucosal lipid membrane. Carrier proteins and channel proteins can assist curcumin to diffuse through the membrane to achieve maximum absorption¹¹.

A child-friendly product that is both safe to use and provides targeted delivery of ingredients is beneficial in the management of URTI. Curkey® is a novel curcumin preparation with improved bioavailability from a unique pastille formulation comprising of a curcumin-protein conjugate, which is intended to dissolve or disintegrate slowly in the mouth. The bioavailability of curcumin in pastille form in the buccal mucosa is reported to be 9 times higher than curcumin in hard gelatin capsules ingested orally. Curkey® pastille remains in contact with the buccal mucosa for a prolonged period of time to provide its desired effect and hence it is the best alternative for traditional remedies which are not child-friendly and cause unnecessary adverse effects. Because the medication does not enter through the digestive system, it avoids first-pass metabolism and boosts the bioavailability of the medication, thus accelerating the onset of action as compared to oral treatment¹³.

The present study evaluated the comparative safety and efficacy of Curkey® pastille when used as a standalone remedy for viral URTI and as an adjuvant with standard care with and without antibiotic treatment in children with bacterial URTIs.

MATERIALS AND METHODS

Study Design :

The present study was an open-label, multi-center, comparative, randomized clinical study to evaluate the efficacy and safety of Curkey® pastille when administered with standard treatment, in acute, viral,

uncomplicated URTIs and in combination with standard antibiotics in acute uncomplicated bacterial URTIs in comparison with standard antibiotic treatment alone in children. The multi-centric study was conducted at Bai Jerbai Wadia Hospital, Mumbai, and Neighbour Care Multispeciality Outpatient Department (OPD) clinic, Ahmedabad as per the clinical trial protocol, reviewed and approved by Institutional Review Board (IRB) and Institutional Ethics Committee (IEC) IEC constituted and functioning in accordance with section 3 of ICH E6 regulation and was registered at the Clinical Trials Registry, India (<https://www.ctri.nic.in/>) with the unique identifier CTRI/2022/05/042564. The IEC approval was received for protocol IEC-BJWHC/SP/2018/07-V4 (Mumbai center) and AZ-C-RMA-17-102 (Ahmedabad center).

Subject Selection :

Eligibility criteria were age between 7 to 12 years; tonsillopharyngitis severity score ≤ 5 ; sore throat pain rated ≥ 66 mm on the sore throat pain intensity scale; fever $> 98.6^{\circ}\text{F}$, the onset of first symptoms of uncomplicated infection and inflammatory disease of the pharynx; willing to sign the informed consent (given by the parent/legal guardian) and participate in the study.

Cases with the following conditions were excluded: history of bronchitis; severe pharyngitis; severe tonsillitis; highly infected and inflamed tonsillitis; gastrointestinal, hepatic, or renal dysfunction; hypersensitivity to aspirin or other nonsteroidal anti-inflammatory drugs and components of Curkey®. Subjects were not enrolled if they exhibited confounding features of URTI such as mouth breathing, dry throat, or coughing. This included cases who had used antibiotics for acute illness in the previous week, or quinolone antibiotics or inhaled therapy in the previous week.

Sample Size Calculation :

A total of 84 subjects was planned to be included in the study to get evaluable for Group A- 12 patients and Group B- 56 patients. For group A, assuming an improvement of 5 points in Tonsillopharyngitis Severity Score (TSS), a sample size of 12 subjects will be required to be recruited for 80% power at the 5% level of significance. Assuming that 20% of the randomized subjects may not be evaluable due to dropout, a total of 20 subjects will be enrolled for this arm. For group B, at a power of 80%, significance level of 5%, $\text{SD}=4$, meaningful clinical difference between groups for the

change in TSS score from baseline to be 3, sample size per arm will be 28, The total number of subjects required across both arms would be 56.

Randomization and Treatment

Screening and randomization were done on Visit 1 (day 1). A total of 69 patients were enrolled, out of which 65 subjects completed the study. Categorization of viral and bacterial infection was made on the basis of symptoms and case history, as per defined criteria¹⁴. Study groups were group A (viral infection) including 11 subjects and group B (bacterial infection) including 56 subjects. Group B was further grouped into two treatment arms, wherein group B1 was randomized with 28 subjects and group B2 was randomized with 26 subjects. Physical examination, prior concomitant medication, vital signs like pulse rate, respiratory rate were recorded.

Group A was administered with test formulation (one Curkey® pastille of 100 mg curcumin), three times a day for the first 2 days followed by one pastille two times for the next 2 days. Group B1 was given amoxicillin 20 mg/kg twice daily for 5 days. Group B2 was given amoxicillin 20 mg/kg twice daily for 5 days and one Curkey® pastille, three times a day for the first 2 days followed by one pastille two times for the next 2 days.

Study Endpoints :

Efficacy endpoints were evaluated on visit 1 (day 1), visit 2 (3±1 day), and visit 3 (5 ±1 day). Visual Analog Scale (VAS) scoring for throat infection, Tonsillo-Pharyngitis Assessment (TPA), and Tonsillopharyngitis Severity Score (TSS) were recorded. The TPA assessed oral temperature, oropharyngeal color, tonsil size, number of oropharyngeal exanthems, number of anterior cervical lymph nodes, maximum tenderness of a few anterior cervical lymph nodes, size of the largest anterior cervical lymph nodes, and size of the anterior cervical lymph nodes. The TSS evaluated sore throat, difficulty in swallowing, increased salivation, and redness of the throat.

The URTI questionnaire, TPA, Sore Throat Pain Intensity Scale (STPIS), Difficulty Swallowing Scale (DSS), and Swollen Throat Scale (SwoTS) were used to assess sore throat discomfort. At presentation, patients were assessed using the URTI questionnaire (nasal congestion, sneezing, runny nose, fever, cough and sore throat). Global Efficacy assessment was carried out using a 5-point scale (1- very good improvement; 2- good improvement; 3- moderate

improvement, 4- negligible improvement; 5- worse). All outcomes were reported by parent/legal guardian in patient diary. All outcomes were reported by principal investigator in case report form.

Global Tolerability assessment was evaluated based on 4 point scale having a rating of 1 as excellent tolerability (No adverse event reported), rating of 2 as good tolerability (Mild adverse event), 3 rating as satisfactory or fair tolerability (Moderate to severe adverse event) and 4 as poor tolerability with severe or serious adverse events. A diary was maintained by the parent/legal guardian to record compliance, and was evaluated on visit 2 (day 3±1) and visit 3 (day 5±1).

Evaluation parameters included a proportion of subjects with a reduction of TSS of 50%, global assessment of efficacy, VAS, and TPA.

Statistical Analysis :

Data was analyzed using SPSS. Randomization was done by using seed 29063 randomization plan such that the design was balanced. For comparison with a group, paired sample t-test was used whereas for comparison between groups, ANOVA test was carried out. Continuous variables were expressed as mean ± Standard Deviation (SD).

RESULTS

Patient Population :

A total of 69 patients with viral and bacterial URTIs were enrolled (44 from the Ahmedabad center and 25 from the Mumbai center), of whom 65 patients completed the study (44 from the Ahmedabad center and 21 from the Mumbai center [two subjects dropped out and two were lost to follow-up]). Group A included 11 children (mean age 8.636 ± 1.748 years), group B1 included 28 children (mean age 8.308 ± 1.258 years), and group B2 included 26 children (mean age 8.615 ± 1.499 years). Table 1 depicts the demographic characteristics of group A and group B subjects on visit 1 and visit 2. Pulse rate, respiratory rate, weight, BMI, and temperature were within the normal range.

Safety Parameters :

The treatment was well tolerated by the patients of all groups. There were no side effects or complications due to Curkey® pastille.

Clinical Condition Based on Symptoms :

Participants in Group A experienced a significant reduction in URTI symptoms such as sore throat,

Table 1 — Demographic characteristics of patients

Demographic characteristics (Mean ± SD) (no of visit)	Group A	Group B1 (Mean ± SD)	Group B2 (Mean ± SD)
Pulse rate (bpm)			
Visit 1	97.455 ± 5.592	76.29±17.661	71.69± 14.704
Visit 2	91.455 ± 7.104	74.31±12.809	70.54± 9.078
Respiratory rate (breaths per minute)			
Visit 1	21.273 ± 1.348	18.07± 3.288	17.77± 2.903
Visit 2	20.818 ± 2.136	17.62± 2.772	17.73± 3.067
Weight (kg)			
Visit 1	27.745 ± 7.612	23.979± 7.2987	23.254± 6.2784
Visit 2	27.764 ± 7.602	22.985± 6.3577	23.238± 6.2708
BMI (kg/m²)			
Visit 1	15.649 ± 2.509	14.2357±2.75697	13.5127±1.84255
Visit 2	15.64 ± 2.502	13.9885± 2.39037	13.4858± 1.8467
Temperature (F)			
Visit 1	97.782 ± 1.425	99.461± 1.3844	99.185± 0.3770
Visit 2	97.391 ± 0.892	97.935± 0.7955	97.996± 0.7252

Note : Data is provided as Mean ± SD.

BMI : Body Mass Index; SD: Standard deviation.

dysphagia, erythema, common cold, sinusitis, and laryngitis at visit 3. URTI symptoms were significantly reduced after 5 days of treatment with Curkey® pastille. Compared with group B1, there was a statistically significant reduction in sore throat, dysphagia, erythema, common cold, sinusitis, and laryngitis in favour of combination therapy in group B2.

Tonsillopharyngitis Severity Score :

Group A treated with Curkey® pastille showed a statistically significant ($P=0.00$) reduction in total TSS by 96.3% on visit 3 from the baseline. Groups B1 and B2 showed reduction in TSS at the end of the treatment. Group B2, treated with Curkey® and antibiotics, showed a statistically significant reduction in TSS by 99.49% on visit 3, whereas group B1 (treated only with antibiotics) showed a reduction in TSS by 97.26% from the baseline ($p=0.806$).

Table 2 — Improvement in STPIS, DSS and SwoTS for the three treatment groups

VAS Parameter	No of visits	Group A (Mean ± SD)	P value	Group B1 (Mean ± SD)	Group B2 (Mean ± SD)	P value (for group B [B1 and B2] between visit 3 and baseline)
STPIS	Visit 1	5.727 ± 2.102	0.00	6.75± 2.562	7.65± 1.231	0.167
	Visit 2	1.909 ± 1.300		2.08± 1.412	2.15± 1.317	
	Visit 3	0.273 ± 0.647		0.14± 0.591	0.00± 0.000	
DSS	Visit 1	5.182 ± 2.483	0.00	6.71± 2.123	7.42± 1.238	0.309
	Visit 2	1.273 ± 1.272		1.81± 1.266	1.81± 1.266	
	Visit 3	0.182 ± 0.603		0.04± 0.189	0.00± 0.000	
SwoTS	Visit 1	6 ± 2.191	0.00	7.21± 1.424	7.15± 1.317	0.987
	Visit 2	1.364 ± 1.206		2.08± 1.354	1.65± 1.056	
	Visit 3	0.273 ± 0.647		0.18± 0.548	0.00± 0.000	

Note : Data is provided as Mean ± SD; DSS: Difficulty Swallowing Scale; SD: Standard Deviation; STPIS: Sore Throat Pain Intensity Scale; SwoTS : Swollen Throat Scale; VAS : Visual Analog Scale.

Visual Analogue Scale Analysis : STPIS, DSS and SwoTS

After 5 days of treatment with Curkey® pastille, Group A showed a significant reduction of 95.20% ($P=0.00$), 96.40% ($P=0.00$) and 95.45% ($P=0.00$) in STPIS, DSS and SwoTS, respectively, from the baseline scores. Reduction of STPIS, DSS and SwoTS values from baseline in group B1 were 97.92%, 99.40%, and 97.50%, respectively. Group B2 showed 100% reduction from the baseline to visit 3 in STPIS, DSS and SwoTS (significant improvement as compared with group B1; Table 2).

Tonsillo-Pharyngitis Assessment (TPA) :

After 5 days of treatment with Curkey® pastille, the TPA scores of group A were reduced. There was a 100% reduction in TPA score at visit 3 for Group B2 (Table 3).

Global Assessment :

For group A, the global assessment of the efficacy of treatment was rated 1 ± 0 and 1.09 ± 0.302 by the investigator and patient, respectively, while the global assessment of tolerability was 1.82 ± 0.751 and 1.64 ± 0.505 by investigator and patient, respectively. Global assessment of efficacy treatment was found to be 1.12 ± 0.326 and 1.15 ± 0.464 for group B2, whereas for group B1 it was found to be 1.11 ± 0.315 and 1.11 ± 0.315 as given by investigator and patient respectively. Tolerability of the treatment for group B1 was found to be highest with 1.14 ± 0.356 and 1.18 ± 0.390 , whereas for group B2 it was found to be the 1.12 ± 0.326 and 1.15 ± 0.368 , by investigator and patient respectively.

DISCUSSION

This prospective, randomized study was intended to investigate the safety and efficacy of Curkey® pastille in children suffering from viral and bacterial URTI's.

Table 3 — Tonsillo-Pharyngitis Assessment

TPA	No of visits	Group A (Mean ± SD)	P value	Group B1 (Mean ± SD)	Group B2 (Mean ± SD)	P value (for group B [B1 and B2] between visit 3 and baseline)
Oral temperature	Visit 1	0.182 ± 0.603	0.34	2.00± 0.609	1.92± 0.484	0.938
	Visit 2	0.091 ± 0.302		0.19± 0.567	0.15± 0.543	
	Visit 3	0 ± 0		0.00± 0.000	0.00± 0.000	
Oropharyngeal color	Visit 1	2.091 ± 302	0.00	2.07± 0.262	2.04± 0.196	0.935
	Visit 2	0.727 ± 0.467		0.62± 0.637	0.46± 0.508	
	Visit 3	0.091 ± 0.302		0.00± 0.000	0.00± 0.000	
Size of tonsils	Visit 1	1.727 ± 0.905	0.00	1.96± 0.429	1.96± 0.445	0.932
	Visit 2	0.727 ± 0.647		0.54± 0.582	0.31± 0.471	
	Visit 3	0.274 ± 0.467		0.07± 0.262	0.00± 0.000	
No of oropharyngeal exanthems	Visit 1	0.545 ± 0.522	0.01	1.11± 0.685	1.19± 0.694	0.957
	Visit 2	0.091 ± 0.302		0.08± 0.272	0.04± 0.196	
	Visit 3	0 ± 0		0.00± 0.000	0.00± 0.000	
Largest size of anterior cervical lymph node	Visit 1	0.091 ± 0.302	0.34	0.46± 0.637	0.42± 0.578	0.992
	Visit 2	0.182 ± 0.405		0.04± 0.196	0.00± 0.000	
	Visit 3	0 ± 0		0.00± 0.000	0.00± 0.000	
No of anterior cervical lymph nodes	Visit 1	0.091 ± 0.302	0.34	0.18± 0.476	0.23± 0.514	0.973
	Visit 2	0.182 ± 0.405		0.04± 0.196	0.00± 0.000	
	Visit 3	0 ± 0		0.00± 0.000	0.00± 0.000	
Maximum tenderness of some anterior cervical lymph nodes	Visit 1	0 ± 0	NA	0.04± 0.189	0.04± 0.196	1.000
	Visit 2	0.091 ± 0.302		0.00± 0.000	0.00± 0.000	
	Visit 3	0 ± 0		0.00± 0.000	0.00± 0.000	

Note : Data is provided as Mean ± SD; SD: Standard Deviation; TPA : Tonsillo-Pharyngitis Assessment.

The most remarkable outcome from the study is that Curkey® pastille is effective at reducing the symptoms of URTI with no adverse reactions. Prior research suggests that, antibiotic usage to treat acute URTI in children has recently increased which weakens their developing immune system, and hence it is important to minimize the frequency of antibiotic use in children. The indiscriminate use of antibiotics has resulted in extensive resistance among microorganisms and re-emergence of old infectious diseases. Therefore, non-synthetic alternatives can be employed in treating infectious ailments independently for viral URTIs or in combination with antibiotics for bacterial URTIs¹⁵. When an antibiotic is no longer effective as a therapeutic drug, synergistic action becomes even more important¹⁶. Curcumin in novel pastille formulations is proven to offer an effective and cost-friendly method of fighting antibiotic-resistant bacteria.

The treatment formulation (Curkey®) of a soft pastille containing 100 mg of curcumin, a potent anti-inflammatory extracted from turmeric, is a concentrated dose with 30× power, since the natural turmeric powder contains only 3-4% curcumin. Furthermore, conventional curcumin exhibits poor bioavailability when consumed orally due to poor gastrointestinal absorption and rapid metabolism. In order to overcome these limitations, Curkey® pastille was formulated with curcumin-protein conjugate that

ensured sustained release of curcumin through the buccal mucosa. Curkey® pastille offers quick relief from soreness, itchiness, swelling, and irritation of the throat, and also builds respiratory immunity to fight viral and bacterial infections. Our study showed improvement in all groups after administration of Curkey® pastille with significant decrease in TSS score at the end of the study.

The TPA, a measure of characteristic clinical symptoms of pharyngitis, affirmed the homogeneity of the diagnosis. The severity of the physical condition causing the sore throat was also validated by measurements on the TPA in the subjects of treatment groups¹⁷⁻¹⁹. Evaluation of TPA was performed at all visits and a significant reduction was observed for all treatment groups after visit 3. The subjects from group A showed significant improvement from the baseline, and group B2 showed rapid improvement in comparison with group B1 for all parameters of TPA.

Furthermore, STPIS, DSS, and SwTS were performed by using VAS to measure discomfort of sore throat. Based on the results, it was demonstrated that Curkey® pastille along with antibiotics provided significant relief from throat discomfort, inflammation, and swelling in comparison to treatment with antibiotics alone. Another important parameter evaluated was the Global Assessment of the efficacy

of the treatment and tolerability, which demonstrated that Curkey® pastille led to symptomatic relief without adverse reactions in any of the treatment groups, indicating a good tolerability.

Based on the questionnaire analysis, we found that all three treatments administered to subjects were effective. The viral sub-group showed significant response within five days of standalone therapy with Curkey® pastille. In the bacterial sub-groups, subjects receiving the combination therapy of Curkey® pastille with antibiotics exhibited significantly quicker improvement of all symptoms of URTI than the bacterial sub-group receiving antibiotics alone.

Our research study confirms that Curkey® pastille is an effective alternative as monotherapy for viral URTI and an excellent adjuvant with antibiotics for bacterial URTIs. The efficacy in reducing symptoms associated with viral and bacterial-infected URTIs can be attributed to its proprietary technology that delivers active curcumin via buccal mucosal absorption, which enhances the bioavailability of curcumin. The compliance to Curkey® pastille was 100%, indicating that the flavor is palatable and acceptable by the pediatric population. One limitation of this study is that data and conclusions were based on a limited population particular to a specific region.

In summary, Curkey® pastille with its proprietary technology enables optimal absorption of curcumin not just in the throat but also through the systemic circulation via buccal absorption. As curcumin only makes up 3% of turmeric, 30 glasses of turmeric milk would be needed to achieve the same results as one Curkey® pastille. Curkey® pastille is an excellent choice in treating viral URTIs independently or in combination with antibiotics for bacterial URTIs. This study provides clinical evidence of significant reduction in viral URTI symptoms within five days of monotherapy with Curkey® pastille that could reduce the irrational usage of antibiotics. In the bacterial sub-groups, the combination therapy of Curkey® pastille with antibiotics exhibited comparatively quicker improvement of all symptoms of URTI than antibiotics alone, making it an effective adjuvant with antibiotics for managing bacterial URTI. The enhanced bioavailability and consumer-friendly formulation makes Curkey® pastille an excellent choice for quicker symptomatic relief in viral and bacterial URTI.

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Conflict of Interest : None

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