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A COMPARATIVE STUDY TO EVALUATE EFFICACY, SAFETY AND COST EFFECTIVENESS BETWEEN ORAL BALOFLOXACIN VS. ORAL LEVOFLOXACIN IN PATIENTS OF ACUTE, UNCOMPLICATED URINARY TRACT INFECTION ATTENDING C. U. SHAH MEDICAL COLLEGE, SURENDRANAGAR

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Keywords:

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ABSTRACT: Objectives: To compare the efficacy, safety and cost effectiveness between oral Balofloxacin and oral Levofloxacin in acute uncomplicated urinary tract infections. **Methods:** Total 130 patients were enrolled for the study, out of them 119 patients completed the study. Patients were divided into two groups randomly; 63 patients received Balofloxacin 100 mg BID orally and 56 patients received Levofloxacin 500 mg orally OD for 5 days. Baseline evaluation of clinical features and urine culture was performed for isolation of causative organism. After 5 days on completion of therapy above parameters were repeated and compared. Analysis of reported adverse drug reactions (ADRs) and cost effectiveness was carried out. **Results:** After completion of treatment clinical evaluation showed Cure rate was 82.54% and 85.71%, while Effective rate was 96.83% and 98.21% for Balofloxacin and Levofloxacin group patients respectively. Bacteriological evaluation revealed that bacteriological clearance rate for Balofloxacin and Levofloxacin was 94.91% and 98.11% respectively. There was no statistical difference between both drugs for clinical and bacteriological cure ($p > 0.05$). ADRs reported were nausea, vomiting, abdominal distension, skin rashes and QT prolongation, with incidence rate of 3.17% and 16.07% for Balofloxacin and Levofloxacin respectively, which was statistically significant ($p < 0.05$). Cost effective analysis revealed that incremental Cost (ΔC) was 30 and incremental effectiveness (ΔE) was -1%, which indicates that Levofloxacin is more cost effective as compared to Balofloxacin. **Conclusion:** Balofloxacin is as efficacious as and safer than Levofloxacin, while Levofloxacin is more cost effective for the treatment of acute uncomplicated urinary tract infections.

INTRODUCTION : Urinary tract infection (UTI) is common with estimated annual global incidence of atleast 250 million cases [1]. About 50 - 60% of the women experience at least one UTI in their life time [2 - 3].

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Acute uncomplicated UTI is defined as UTI in a person with structurally and functionally normal urinary tract [4]. Uropathogenic *Escherichia coli* (*E. coli*) is strongly associated with all acute uncomplicated UTI [5].

Other uropathogens causing acute uncomplicated UTI are *Staphylococcus saprophyticus* in 5 - 10%, Klebsiella, Proteus mirabilis, group b streptococcus and other organisms in <5% [6 - 7]. As recommended by several guidelines and reviews, today the most popular antibiotics for acute uncomplicated UTI are Fluroquinolones (FQ) [8 - 10].

Levofloxacin is the second generation FQ which acts by inhibiting bacterial DNA gyrase and topoisomerase IV, thus inhibiting tertiary negative supercoiling of bacterial DNA. Adverse effects of Levofloxacin are nausea, vomiting, headache, dizziness, skin rash, QT prolongation, Photosensitivity and CNS side effects [11]. At present, Levofloxacin is one of the most commonly used FQ due to increased resistance to first generation FQ [12]. Balofloxacin is an orally active Fluroquinolone antibiotic which has been developed for the treatment of UTI, further more urinary excretion of Balofloxacin is 86% which is favourable for treatment in UTI [13]. *In vivo* antibacterial activity of Balofloxacin against anaerobic bacteria and *Staphylococcus aureus* (*S. aureus)* is better than levofloxacin, ciprofloxacin and Ofloxacin [14].

Addition of a 3-methylaminopyridine at C-7 and a methoxy substituent at C-8 of the quinolone nucleus differentiates it from other Fluroquinolone compounds [15]. These changes has provided benefits of high anti-anaerobic activity, non-photo toxicity, decreased CNS side effects and decreased resistance probability [16 - 18]. There are *in vitro* and *in vivo* studies suggesting Balofloxacin as a potential alternative of current medical management of acute uncomplicated UTI, but very few studies have been done to compare it with Levofloxacin which is also a potential agent [19 - 20]. So this study was designed to compare efficacy, safety and cost-effectiveness between these potential drugs in acute uncomplicated UTI.

MATERIALS AND METHODS: The study was approved by Institutional Ethics Committee (H), C. U. Shah Medical College and Hospital (CUSMC and H), Surendranagar. The study was prospective, open label, randomised and comparative in nature. Total 130 patients were enrolled for the study from that 11 patients lost the follow up, so finally 119 completed the whole study. Newly diagnosed adult patients of acute uncomplicated UTI of either gender at Medicine, Surgery or Gynaecology department of CUSMC and H, Surendranagar were included in the study. Informed consent was taken from the each patient before participation in the study. Clinical diagnosis was done by clinicians of respective department on the basis of history and clinical features suggestive of acute uncomplicated UTI, which are dysuria, increased urinary frequency, supra-pubic pain and urgency with onset of not more than 10 days before enrolment. Presences of ≥ 2 clinical features were considered as significant. Patients with following criteria were excluded from the study:

1) Suspicion of complicated UTI (presence of fever above 38 °C, flank pain, known urologic structural abnormality) or prostatitis. 2) History suggesting Symptoms of UTI for more than last 10 days. 3) Evidence of predisposing factor to UTI (*e.g.* calculi, stricture, primary renal disease like polycystic renal diseases and neurogenic bladder). 4) Pregnant, breast-feeding women. 5) Use of systemic Antibiotic within last 48 hours before enrolment. 6) Patients unable to take oral medications on outpatient basis.

After clinical diagnosis was made, urine of patient was collected for bacteriological diagnosis and sent to the Microbiology department of the CUSMC and H. Culture indicating ≥ 10000 colony forming units (CFU)/ml alone or ≥ 1000 CFU/ml + Pyuria> 10 pus cells/HPF was stated as positive urine culture [21] and organism was isolated. Patients who had shown no isolation on culture, but had significant clinical features were included in the study. QT interval of each patient was noted by using digital ECG (Electrocardiogram) machine.

Patients were randomly divided into two treatment groups. Group 1 received oral Balofloxacin 100 mg twice in a day and Group 2 received oral Levofloxacin 500 mg once in a day for 5 days. Patients were advised to come for follow up at the end of therapy after an interval of 5 days. After completion of therapy above parameters of clinical features, urine culture and QT interval were repeated.

Outcome was Measured by two Parameters:
1) Clinical cure and 2) Bacteriological cure.

Clinical Cure: Clinical cure was assessed on follow up according to Antibacterial drug clinical research guidelines [14]. According to this guideline patients were divided into following categories: Recovered: Complete disappearance of all baseline clinical features on follow up. Having an effect: Resolution or reduction in more than or equal to 50% of clinical features on follow up. Progress:

Resolution or reductions in less than 50% of clinical features on follow up. Failure: Persistence of baseline clinical features on follow up. Cure rate was calculated by considering patients under Recovered category, while Effective rate was indicated by total sum of patients under Recovered and Having an effect categories.

Bacteriological Cure: When patients were declared cured clinically, urine was collected and cultured. If it showed no growth of isolated organism and no growth of new organism, patients were declared bacteriologically cured. Bacteriological clearance was defined as percentage of bacteriologically cured patients.

Patients were asked for any adverse effect during the course of treatment. Corrected QT interval of > 0.45 seconds on follow up was stated as prolongation of QT interval. CDSCO (Central drug standard control organization) ADR (Adverse Drug Reaction) reporting form was filled up for patient with any adverse effect. Analysis of reported ADR was done by WHO causality assessment scale in to following categories: Certain, Probable, Possible, Unlikely, Unclassified and Unassessible [22].

Cost Effectiveness: [23] The cost effectiveness was calculated on the basis of total expenditure incurred on medicines plus cost of conveyance at the end of treatment in Rs, and Effective rate in percentage. Total cost of treatment = Cost in Rs for first visit + Cost in Rs for follow up. Incremental cost (Δ C) (in Rs) = Cost of new treatment (Balofloxacin) – Cost of old treatment (Levofloxacin). Incremental effectiveness (Δ E) (in %) = Effective rate of new treatment (Balofloxacin) – Effective rate of old treatment (Levofloxacin).

Statistical Analysis: MedCalc software version 7.6.0.0 was used for all statistical analysis. Association between two groups in baseline distribution of gender, Cure rate, Effective rate, bacteriological clearance and incidence of ADRs was established by Chi square test (X^2). ($p < 0.05$ was kept as significant in all statistical analysis).

RESULTS: Total 130 were enrolled in the study out of them, 06 patients from Balofloxacin group and 05 patients from Levofloxacin group were lost to follow up. So, finally 119 completed the study. Out of 119 patients 63 were treated with Balofloxacin, while 56 were prescribed Levofloxacin.

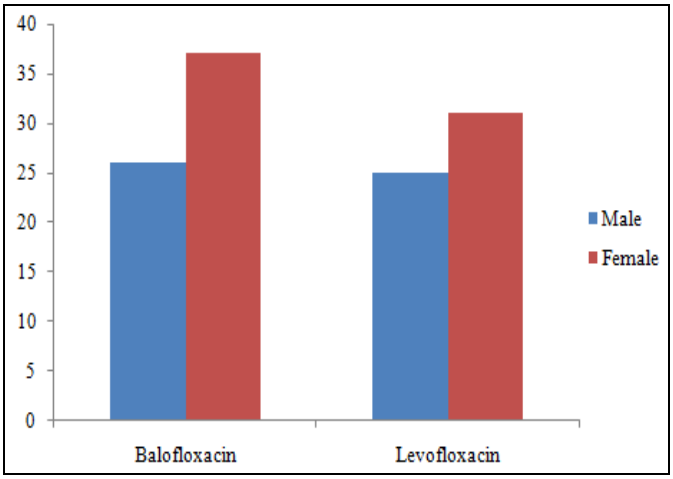

FIG. 1: GENDER WISE DISTRIBUTION OF THE POPULATION

Fig. 1 displays that in Balofloxacin treated group numbers of male and female were 26 (41.27%) and 37 (58.73%) respectively; while in Levofloxacin group 25 (44.64%) male and 31 (55.36%) female patients were treated. It is evident that female patients were more in both groups. Evaluation of the baseline characteristics of the patients showed that there was no significant difference between both the groups in gender. ($X^2 = 0.03$, df = 1, $p > 0.05$).

TABLE 1: MICRO-ORGANISMS ISOLATED

Micro-organism	Balofloxacin	Levofloxacin	Total
E. coli	47 (74.60%)	39 (69.64%)	86 (72.27%)
Klebsiella	03 (4.76%)	05 (8.93%)	08 (6.72%)
Pseudomonas	05 (7.94%)	02 (3.57%)	07 (5.88%)
Staph. aureus	04 (6.78%)	05 (8.93%)	09 (7.56%)
MRSA	00 (6.35%)	02 (3.57%)	02 (1.68%)
No Growth	04 (6.78%)	03 (5.36%)	07 (5.88%)
Total	63	56	119

Table 1 display that *E. coli* was the most common bacteria causing acute uncomplicated UTI in our study. Rate of the population infected by *E. coli* was 72.27%. It was followed by *S. aureus* (7.56%), Klebsiella (6.72%), Pseudomonas (5.88%) and MRSA (1.68%). Total 7 patients did not show any growth of Micro-organisms on urine culture.

TABLE 2: CLINICAL CURE ANALYSIS

Group	Recovered	Having an effect	Progress	Failure
Balofloxacin (n = 63)	52 (82.54%)	09 (14.29%)	02 (3.17%)	00 (0.0%)
Levofloxacin (n = 56)	48 (85.71%)	07 (12.5%)	01 (1.79%)	00 (0.0%)

Table 2 shows analysis of clinical effect between both groups for total cases of 119. It reveals that in patients treated with Balofloxacin out of 63 patients, 52 fall under "Recovered", 09 in "Having an effect" and 02 in "Progress", as compared to Levofloxacin treated patients in which, out of 56 patients, 48 fall under "Recovered", 07 in "Having an effect" and 01 in "Progress". Now, as described in methods Clinical cure analysis showed Cure rate for Balofloxacin and Levofloxacin was 82.54% (52/63) and 85.71% (48/56) respectively, which showed no significant difference ($X^2 = 0.04$, df = 1, $p > 0.05$). Effective rate was 96.83% (61/63) for Balofloxacin as compared to 98.21% (55/56) for Levofloxacin. Applying Chi square test indicates no significant difference in both the drugs for Effective rate. ($X^2 = 0.01$, df = 1, $p > 0.05$).

TABLE 3: BACTERIOLOGICAL CURE ANALYSIS

Group	No. of culture positive before treatment	No. of culture negative after treatment	Bacteriological clearance (In %)
Balofloxacin	59 (93.65%)	56	94.91%
Levofloxacin	53 (94.64%)	52	98.11%

Table 3 reveals that in Balofloxacin group 59 cultures out of 63, while in Levofloxacin group 53 cultures out of 56 were positive indicating 93.65% and 94.64% culture positivity respectively. After treatment, in Balofloxacin treated patients, 56 out of 59 cultures became negative as compared to 52 out of 53 cultures of Levofloxacin treated patients, which shows Bacteriological clearance of 94.91% and 98.11% for Balofloxacin and Levofloxacin respectively. There was no significant difference between both in bacteriological clearance ($X^2 = 0.16$, df = 1, $p > 0.05$).

TABLE 4: SUMMARY OF CLINICAL CURE AND BACTERIOLOGICAL CURE IN BOTH GROUPS

Outcome measure	Parameter	Balofloxacin	Levofloxacin
Clinical cure	Cure rate	82.54%	85.71%
	Effective rate	96.83%	98.21%
Bacteriological cure	Bacteriological clearance	94.91%	98.11%

Table 4 displays overall summary of Clinical and Bacteriological cure in both groups. It collectively reflects all the rates for both the drug groups. Clinical cure is indicated by Cure rate and Effective rate, while Bacteriological cure is reflected by Bacteriological clearance. It is evident from these results that for clinical and Bacteriological cure, which are indicators of efficacy, there is no significant difference between both the drug groups.

TABLE 5: COMPARISON OF CLINICAL CURE BETWEEN TWO DRUGS ACCORDING TO INFECTIVE MICRO-ORGANISMS

Micro-organism	Balofloxacin (n = 63)					Levofloxacin (n = 56)				
	Recovered	Having an effect	Progress	Failure	Total	Recovered	Having an effect	Progress	Failure	Total
E. coli	41	05	01	00	47	37	02	00	00	39
Klebsiella	02	01	00	00	03	04	01	00	00	05
Pseudomonas	04	01	00	00	05	02	00	00	00	02
S. aureus	03	00	01	00	04	04	01	00	00	05
MRSA	00	00	00	00	00	00	01	01	00	02
No. Growth	02	00	02	00	04	01	02	00	00	03
Total	52	07	04	00	63	48	07	01	00	56

Table 5 displays organism wise clinical effect in both groups. It reflects that from the patients infected with various Microorganisms, majority of them (59/63 in Balofloxacin group and 55/56 in Levofloxacin group) were in either "Recovered" or "Having an effect" categories, which were the criteria for evaluating clinical cure. In "Progress" category of Balofloxacin treated patients, 1 was infected with *E. coli*, 1 with *S. aureus* and 2 were without any growth of Microorganism, while only 1 patient infected with MRSA was in "Progress" from Levofloxacin treated patients. None of the patient from either group falls under "Failure" category.

Cost - Effectiveness between Oral Balofloxacin and Oral Levofloxacin: Average Cost of Balofloxacin 100 mg tablet is Rs 7, Levofloxacin 500 mg tablet is Rs 8 and average cost of conveyance per subject is Rs 80.

TABLE 6: TOTAL AND PER PATIENT COST OF THERAPY

Cost (In Rs)	Balofloxacin	Levofloxacin
Total cost of therapy	4410	2240
Cost of conveyance	5040	4480
Total cost	9450	6720
Cost per subject	150	120
Effective rate	97%	98%

Table 6 displays summation of all costs including follow up as mentioned in materials and methods. It illustrates that total cost of therapy per subject is more in Balofloxacin as compared to levofloxacin. Effective rate is more in Levofloxacin as compared to Balofloxacin.

Now, Incremental cost (ΔC) = Cost of new treatment (Balofloxacin) – Cost of old treatment (Levofloxacin). Incremental Effectiveness (ΔE) = Effective rate of new treatment (Balofloxacin) – Effective rate of old treatment (Levofloxacin). So, Incremental cost (ΔC) and incremental effectiveness (ΔE) between Balofloxacin and levofloxacin are Rs 30 and -1% respectively.

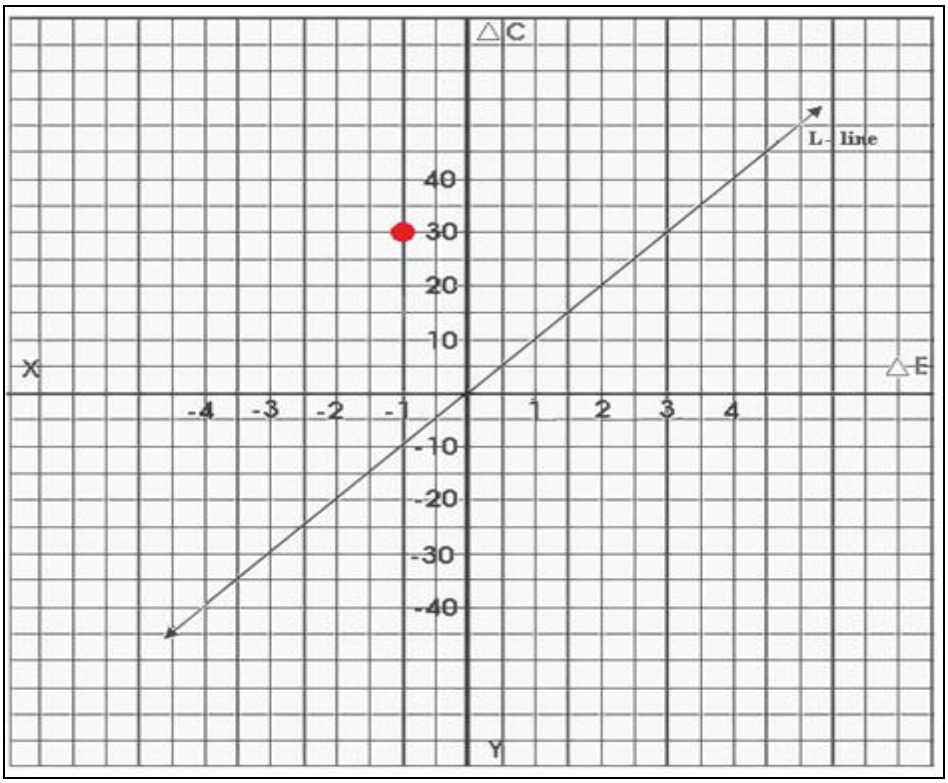

FIG. 2: GRAPH BETWEEN Δ E⟶ Δ C

Fig. 2 displays the graph between ΔE and ΔC. A line passing from 0 is L line. The zone above L line is known as un-acceptable zone, while zone below the L line is known as acceptable zone. In our study point of intersection lies in the unacceptable zone which suggests that Levofloxacin is more cost effective than Balofloxacin.

Assessment of Safety in both Groups: Incidence of ADRs in Balofloxacin treated patients was 3.17% (02/63) as compared to 16.07% (9/56) in Levofloxacin treated patients.

TABLE 7: ADRS REPORTED DURING TREATMENT WITH WHO CAUSALITY ASSESSMENT

ADRs	Balofloxacin (n=2)	Levofloxacin (n=9)*
Nausea & Vomiting	01 (Certain)	02 (Certain)
Diarrhoea	00	02 (Certain)
Abdominaldis tension	01 (Probable)	00
QT Prolongation	00	02 (Probable)
Skin rash	00	03 (2 Certain, 1 Possible)

Value with * is significant at $p < 0.05$).

Table 7 displays various ADRs reported on follow up after the treatment. Statistical analysis by Chi square test showed significant difference between both drugs in reported ADRs. ($X^2 = 4.44$, df = 1, $p < 0.05$).

DISCUSSION: This study showed that Balofloxacin and Levofloxacin produced significant effect in treatment of acute uncomplicated UTI. Most of the studies of UTI focus on bacteriological cure only, but present study also highlights symptoms and clinical outcome. *E. coli* is the most common micro-organism causing acute uncomplicated UTI followed by *S. saphrophyticus*, Klebsiella, Proteus and group b streptococci [5 - 7]. In our study *E. coli* was the leading causative agent followed by *S. aureus*, Klebsiella, Pseudomonas and MRSA. This difference might be due to geographical variation of micro-organisms.

The results of the study reflect that clinical cure rate for Balofloxacin and Levofloxacin was 82.54% and 85.71% respectively, while Effective rate was 96.83% and 98.21% respectively, which showed no significant difference ($p > 0.05$) between both the drugs in the clinical effect. Yao G *et al*., [24] showed clinical cure rate of 77.1% and 81.8%, while effective rate of 96.2% and 97.3% for Balofloxacin and Levofloxacin respectively with no significant difference. This supports results of this study.

Zhang D *et al*., [25] reported Bacteriological clearance rate for Balofloxacin and Levofloxacin was 93.18% and 90.70% respectively with no significant difference. It is evident from results of present study that bacteriological clearance rate was 94.91% and 98.11% for Balofloxacin and Levofloxacin respectively, which is more than above mentioned study, but reflecting no significant difference between both drugs in bacteriological clearance. Cost effective analysis of this study showed that Levofloxacin was more cost effective as compared to Balofloxacin; however we could not found similar cost effectiveness study for comparison.

Main adverse reactions were leukopenia, GIT disturbances, elevated conjugated bilirubin and abnormal urine; there was no significant difference between two groups [25]. The incidence of adverse reaction was 8.2% *vs*. 8.9% ($p > 0.05$) for both groups including nausea, vomiting, diarrhoea and elevated transaminase [24]. Incidence rate of ADRs was 4.8% and 0.9% for Balofloxacin and Levofloxacin treated patient respectively with no significant difference [14].

In present study in Balofloxacin treated group, 1 patient reported nausea, vomiting and 1 complained of abdominal distension indicating incidence rate of 3.17%, while in Levofloxacin treated patients, 2 patients reported with nausea and vomiting, 2 complained of diarrhoea, 2 developed QT prolongation and 3 came with skin rashes and reported incidence rate was 16.07%. In contrast to above 3 studies, present study showed statistically significant difference ($p < 0.05$), which indicates that Balofloxacin is significantly safer as compared to Levofloxacin. In this study, WHO causality assessment of reported ADRs was also carried out, which revealed that out of 11 ADRs, 7 were certain, 3 were probable while 1 was possible. Comparatively smaller sample size was the limitation of this study. Further studies are warranted to compare efficacy and safety between Levofloxacin and Balofloxacin in acute uncomplicated urinary tract infections.

CONCLUSION: From the results and discussion we conclude that Balofloxacin is as efficacious as and safer than Levofloxacin, while Levofloxacin is more cost effective for the treatment of acute uncomplicated urinary tract infections.

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CONFLICTS OF INTEREST: Nil

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