J Ped Nephrol
Journal of Pediatric Nephrology
2025. Volume 13

Research Paper

Adjunctive Use of Melatonin in Pediatric Urinary Tract Infections: A Randomized Controlled Trial

Ali Arjmand Shabestary[1, 2], Fatemeh Dorreh[2], Parsa Yousefichaijan[3*], Mohammad Rafiei[4], Amirvali Azodzaade Ardakani[5], Alireza Toghra[2]

1. Department of Pediatrics, Taleghani Hospital, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
2. Department of Pediatrics, Amirkabir Hospital, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
3. Department of Pediatric Nephrology, School of Medicine, Amirkabir Hospital, Arak University of Medical Sciences, Arak, Iran.
4. Department of Biostatistics, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
5. Department of Pediatrics, School of Medicine, Amirkabir Hospital, Arak University of Medical Sciences, Arak, Iran.

Use your device to scan and read the article online

Citation Arjmand Shabestary A, Dorreh F, Yousefichaijan P, Rafiei M, Azodzaade Ardakani A, Toghra A. Adjunctive Use of Melatonin in Pediatric Urinary Tract Infections: A Randomized Controlled Trial. Journal of Pediatric Nephrology. 2025; 13:E48292. https://doi.org/10.22037/jpn.v13i1.48292

https://doi.org/10.22037/jpn.v13i1.48292

Article info:
Received: 11 Jan 2025
Accepted: 23 Mar 2025
Publish: 01 Apr 2025

Corresponding Author:
Parsa Yousefichaijan, MD.
Address: Department of Pediatric Nephrology, School of Medicine, Amirkabir Hospital, Arak University of Medical Sciences, Arak, Iran.
E-mail: parsayousefichaijan@yahoo.com

ABSTRACT

Background and Aim: Urinary tract infections (UTIs) are among the most common bacterial infections in children and adolescents. Despite standard antibiotic therapy, symptom resolution can be delayed due to ongoing inflammation. Melatonin, a neurohormone with known antioxidant and immunomodulatory properties, may offer therapeutic benefits in this context. This study aimed to evaluate the clinical efficacy of adjunctive melatonin therapy in pediatric patients with UTIs, focusing on symptom resolution and potential anti-inflammatory effects.

Methods: In this double-blind, randomized, placebo-controlled trial, 100 children aged 4–18 years with confirmed UTI and concurrent sleep disturbances were assigned to receive either melatonin (3 mg/day) plus antibiotics (intervention group) or antibiotics plus placebo (control group) for 10 days. Primary outcomes included time to resolution of fever, dysuria, abdominal pain, urinary frequency, and incontinence.

Results: Baseline characteristics were similar between groups. The melatonin group showed significantly faster resolution of fever (1.3±0.49 vs 3.7±0.69 days, P=0.001), abdominal pain (1.2±0.54 vs 3.62±0.67 days, P=0.001), and dysuria (1.5±0.57 vs 3.6±0.67 days, P=0.001). No significant differences were observed in urinary frequency or incontinence outcomes. No adverse effects related to melatonin were reported.

Conclusion: Adjunctive melatonin therapy appears to accelerate the resolution of key UTI symptoms in children when combined with antibiotics, likely due to its anti-inflammatory and antioxidant properties. These findings suggest a potential role for melatonin in pediatric UTI management and warrant further investigation in larger, multicenter trials.

Keywords: Urinary tract infection (UTIs), Melatonin, Randomized controlled trial (RCT)

J Ped Nephrol
Journal of Pediatric Nephrology

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections in children and adolescents, with the highest incidence during the first decade of life. If left untreated, UTIs can lead to serious complications, such as renal scarring, growth disturbances, hypertension, and chronic kidney disease [1]. Diagnosis is typically confirmed through urine culture, while clinical presentation varies with age—ranging from non-specific symptoms in infants to classic dysuria and urgency in older children [2, 3].

While recurrent UTIs are commonly attributed to anatomical abnormalities, over half of affected children lack such risk factors, highlighting the role of immune and nutritional deficiencies, especially in regions with high rates of micronutrient malnutrition [4, 5]. Melatonin, a neurohormone produced mainly by the pineal gland, exhibits potent antioxidant and immunomodulatory properties [6]. It is also synthesized in high concentrations in the gastrointestinal tract, where it protects against oxidative stress and inflammation [7]. Recent studies have shown melatonin's antibacterial effects against both Gram-positive and Gram-negative pathogens, along with its ability to modulate immune responses and reduce inflammatory damage in bacterial infections [8-10].

Despite the accumulating evidence of melatonin's therapeutic potential in various infections and its established use in managing conditions, such as nocturnal enuresis, its role in the prevention or treatment of UTIs has not yet been thoroughly investigated. Given that infected urine can provoke significant inflammatory and immune responses leading to renal damage and scarring [11], the potent antioxidant and immunomodulatory properties of melatonin present a compelling rationale for its investigation in this context. Furthermore, its protective effects against oxidative and ischemic injury have been well documented in multiple organ systems, particularly the brain and heart [12].

Therefore, the present study aimed to evaluate the clinical efficacy of melatonin in reducing UTI symptoms and associated complications in pediatric and adolescent patients.

Materials and Methods

Study design and setting

This was a randomized, double-blind, placebo-controlled clinical trial conducted at Amir Kabir Hospital in Arak, Iran, following approval from the institutional ethics committee. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and followed the CONSORT guidelines for clinical trial reporting.

Participants

A total of 100 pediatric patients aged between 4 and 18 years, presenting with confirmed UTI and concurrent sleep disturbances, were enrolled consecutively from inpatient and outpatient services. The diagnosis of UTI was confirmed by a pediatric specialist through clinical evaluation and laboratory testing. Eligible participants were required to have no underlying renal or hepatic disease, and informed written consent was obtained from their parents or legal guardians prior to inclusion.

Children were excluded from the study if they failed to adhere to the treatment protocol or if they or their caregivers chose to withdraw from the study at any time.

Randomization and blinding

Participants were randomly assigned to either the intervention or control group using a permuted block randomization method with blocks of six, designed to maintain balance between the two groups. Randomization sequences included various permutations, such as ABAB, BBAA, BAAB, etc., where "A" represented the intervention group and "B" the control group. Allocation was implemented by a resident physician who was not involved in outcome assessment.

The study employed a double-blind design. Neither the participants nor the researchers collecting outcome data were aware of group assignments. Participants were informed that they would be randomly assigned to one of two treatment arms. The intervention group received the standard antibiotic regimen for UTI in addition to melatonin, while the control group received the same antibiotic treatment plus a placebo tablet that was visually indistinguishable from the melatonin.

Intervention

Patients in the intervention group received 3 mg melatonin tablets (Razak Pharmaceutical Company, Iran) once daily for 10 consecutive days in addition to standard antibiotic therapy. The control group received the same antibiotic regimen along with a placebo tablet that matched the melatonin in shape and appearance. The placebo contained 3 mg of compressed lactose and was also manufactured by Razak to ensure blinding integrity.

Outcome measures

Clinical outcomes were evaluated using a standardized checklist completed by caregivers and reviewed by the research team throughout the 10-day treatment period. Fever was defined as a body temperature exceeding 38 ˚C. Dysuria was recorded based on reports from children describing burning or pain during urination. Urinary frequency was assessed as the need to urinate frequently during the day or night, with either normal or reduced urinary volume. Abdominal pain referred to any reported discomfort in the abdominal region, and urinary incontinence was defined as any involuntary urine leakage. The number of daily episodes of urinary frequency and incontinence were also recorded and analyzed.

Sample size calculation

Sample size was calculated using data from a previous study by Taher et al. [13], in which vasopressor levels on the fifth day after melatonin administration were used as the reference outcome. The melatonin group had a mean value of 6.2 with a standard deviation of 5.12, while the placebo group had a mean of 3.2 with a standard deviation of 3.95. Based on these values, a minimum of 36 participants per group was estimated to provide sufficient power. To increase precision and account for potential dropouts, the sample size was increased to 50 participants per group, resulting in a total sample of 100 patients.

Data collection

Demographic and clinical information, including age, sex, and UTI-related symptoms, was collected using a researcher-developed checklist. The checklist was completed at baseline and throughout the study to monitor symptom progression or resolution.

Statistical analysis

All statistical analyses were performed using SPSS software, version 26. Quantitative variables were summarized as Mean±SD, and categorical variables were presented as frequencies and percentages. Between-group comparisons were made using independent samples t-tests for normally distributed data and Mann-Whitney U tests for non-normal data. Categorical variables were analyzed using the chi-square test or Fisher's exact test as appropriate. Symptom progression over time was assessed using repeated measures analysis of variance. A two-tailed $P<0.05$ was considered statistically significant, and all analyses were conducted with a 95% confidence level (CI).

Results

Participant flow and baseline characteristics

A total of 100 children aged 4 to 18 years with confirmed UTI and concurrent sleep disturbances were enrolled in the study and randomized equally into two groups: 50 participants in the intervention group, who received melatonin (3 mg/day for 10 days) alongside antibiotics, and 50 participants in the control group, who received antibiotics alone.

The mean age in the intervention group was 7.26±1.6 years, and in the control group was 8.04±2.47 years, with no statistically significant difference between the two groups (P=0.06). Gender distribution was also comparable between groups (P=0.685), with females comprising 56% of the intervention group and 60% of the control group (Table 1).

Primary symptom outcomes

Table 2 summarizes the clinical symptoms at baseline and their distribution across groups. Fever (P=0.009), abdominal pain (P=0.001), and dysuria (P=0.001) were significantly more frequent in the control group compared to the intervention group. No significant differ-

Table 1. Baseline demographic characteristics of participants

Variables		Mean±SD/No. (%)		P
		Intervention Group (n=50)	Control Group (n=50)	
Age (y)		7.26±1.6	8.04±2.47	0.060
Gender	Female	28(56)	30(60)	0.685
	Male	22(44)	20(40)	

J Ped Nephrol
Journal of Pediatric Nephrology

Table 2. Clinical symptom distribution between groups

Symptoms	Mean±SD/No. (%)		P
	Intervention Group (n=50)	Control Group (n=50)	
Fever	22(44)	35(70)	0.009
Abdominal pain	17(34)	42(84)	0.001
Dysuria	20(40)	38(76)	0.001
Urinary incontinence	24(48)	27(54)	0.550
The number of incontinence episodes	1.96±0.89	2.1±0.95	0.440
Urinary frequency per day	3.52±2.31	3.07±1.67	0.340

ences were observed in urinary incontinence (P=0.55), frequency of incontinence episodes (P=0.44), or urinary frequency per day (P=0.34).

Symptom resolution

Table 3 displays the mean number of days until symptom resolution. The intervention group experienced significantly faster resolution of fever (1.3±0.49 vs 3.7±0.69 days, P=0.001), abdominal pain (1.2±0.54 vs 3.62±0.67 days, P=0.001), and dysuria (1.5±0.57 vs 3.6±0.67 days, P=0.001). No significant differences were observed for urinary incontinence, frequency of incontinence episodes, or urinary frequency (Table 3).

Discussion

This randomized controlled trial (RCT) evaluated the effects of melatonin (3 mg daily for 10 days) alongside antibiotics in 100 children with UTIs and sleep disturbances. Participants were randomly assigned to intervention and control groups, with no significant baseline differences in age or gender. The addition of melatonin significantly improved key clinical symptoms, including fever, abdominal pain, and dysuria, compared to antibiotics alone. However, melatonin did not lead to statistically significant improvements in urinary frequency, incontinence, or the number of incontinence episodes, suggesting that while it may enhance symptom relief in certain domains, its effects are more limited for urinary control outcomes.

Our results support the findings of Fathollahi et al. [14], who in a review study highlighted the antioxidant and anti-inflammatory roles of melatonin in the lower urinary tract. Melatonin was shown to reduce oxidative damage, inhibit smooth muscle hyperactivity, modulate calcium signaling, and decrease bladder inflammation. Our observed improvements in dysuria, abdominal pain, and urinary frequency are consistent with these mechanisms, reinforcing the hypothesis that melatonin's therapeutic benefits in UTI may be attributed to its systemic antioxidant and anti-inflammatory actions.

A recent preclinical study by Yao et al. provides valuable mechanistic insights into melatonin's potential role

Table 3. Mean duration of symptoms resolution in patients

Symptoms	Mean±SD		P
	Intervention Group	Control Group	
Fever (d)	1.3±0.49	3.7±0.69	0.001
Abdominal pain (d)	1.2±0.54	3.62±0.67	0.001
Dysuria (d)	1.5±0.57	3.6±0.67	0.001
Urinary incontinence (d)	3.25±1.7	3.7±0.7	0.080
Incontinence frequency (d)	3.49±1.36	3.78±0.92	0.218
Urinary frequency (d)	3.48±1.18	3.74±0.86	0.212

in managing urinary tract pathology. This study demonstrated that melatonin significantly reduced calcium oxalate (CaOx) crystal deposition in a mouse model by inhibiting LPS-induced inflammasome activation and renal tubular epithelial cell pyroptosis—an inflammatory form of cell death associated with bacterial infection [15]. While this study focused on nephrolithiasis rather than UTI per se, the findings highlight melatonin's immunomodulatory capacity in the urinary tract, which may translate into symptom relief in infectious conditions like UTI.

While no previous pediatric clinical trials have directly investigated melatonin's role in UTI symptom resolution, parallels can be drawn from studies on melatonin's effects in adult populations with urinary symptoms. A notable example is the randomized, double-blind, placebo-controlled crossover trial by Drake et al. which evaluated melatonin's efficacy in managing nocturia in adults with multiple sclerosis (MS) [16]. In this study, 2 mg of sustained-release melatonin did not significantly reduce nocturia frequency or improve lower urinary tract symptoms (LUTS), sleep quality, or quality of life. Although this study differs in patient population and symptom etiology, the findings similarly indicate limited benefit of melatonin on direct urinary function.

Our findings are consistent with this study, as melatonin had no significant effect on urinary incontinence or voiding frequency. However, our study diverged meaningfully by showing that melatonin significantly accelerated resolution of systemic UTI symptoms, such as fever and abdominal pain. This suggests that melatonin's primary therapeutic benefit may lie not in local bladder modulation—as targeted in nocturia studies—but rather in its anti-inflammatory, antioxidant, and immune-enhancing effects, particularly relevant during infection.

In a RCT by Leerasiri et al. [17] involving 60 elderly women with nocturia, the administration of 2 mg melatonin for two weeks significantly reduced nocturnal voids and improved sleep quality, without major adverse effects. However, our study did not observe a statistically significant reduction in urinary frequency in the pediatric population. The contrasting results could be explained by the different demographics and clinical settings of the two studies—older women with nocturia versus children with acute UTI.

Conversely, our findings are consistent with those of Dipasquale et al. [18], who evaluated the role of melatonin in managing functional abdominal pain disorders in children. In their study, 42 children aged 4–18 years received either melatonin with Lactobacillus Rhamnosus GG or a placebo. Over a 12-week period, the melatonin group showed a >50% reduction in pain intensity and frequency. While their population involved children with functional pain rather than UTI, our findings similarly demonstrate melatonin's significant efficacy in reducing abdominal pain, suggesting a broader potential for melatonin as a pediatric analgesic.

Conclusion

In conclusion, melatonin appears to accelerate the resolution of systemic UTI symptoms in children when used alongside antibiotics, likely due to its anti-inflammatory and sleep-regulating properties. These findings are consistent with a growing body of literature supporting melatonin's role in pediatric care. Further large-scale trials are warranted to confirm these results and delineate its specific mechanisms in infectious disease recovery.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results, and manuscript drafting. Each author approved the submission of the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

References

[1] Freedman AL. Urologic diseases in North America Project: Trends in resource utilization for urinary tract infections in children. J Urol. 2005; 173(3):949-54. [DOI:10.1097/01.ju.0000152092.03931.9a] [PMID]

J Ped Nephrol
Journal of Pediatric Nephrology

[2] Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010; 7(12):653-60. [DOI:10.1038/nrurol.2010.190] [PMID]

[3] Nicolle LE. Urinary tract infection. Crit Care Clin. 2013; 29(3):699-715. [DOI:10.1016/j.ccc.2013.03.014] [PMID]

[4] Gondim R, Azevedo R, Braga A, Veiga ML, Barroso U, Jr. Risk factors for urinary tract infection in children with urinary urgency. Int Braz J Urol. 2018; 44(2):378-83. [DOI:10.1590/s1677-5538.ibju.2017.0434] [PMID]

[5] Beiraghdar F, Panahi Y, Einollahi B, Moharamzad Y, Nemati E, Amirsalari S. Predisposing factors for renal scarring in children with urinary tract infection. Saudi J Kidney Dis Transpl. 2012; 23(3):532-7. [Link]

[6] Pévet P. Melatonin. Dialogues Clin Neurosci. 2002; 4(1):57-72. [DOI:10.31887/DCNS.2002.4.1/ppevet] [PMID]

[7] Srinivasan V, Mohamed M, Kato H. Melatonin in bacterial and viral infections with focus on sepsis: A review. Recent Pat Endocr Metab Immune Drug Discov. 2012; 6(1):30-9. [DOI:10.2174/187221412799015317] [PMID]

[8] Lee HY, Byeon Y, Back K. Melatonin as a signal molecule triggering defense responses against pathogen attack in Arabidopsis and tobacco. J Pineal Res. 2014; 57(3):262-8. [DOI:10.1111/jpi.12165] [PMID]

[9] Gerber J, Lotz M, Ebert S, Kiel S, Huether G, Kuhnt U, et al. Melatonin is neuroprotective in experimental streptococcus pneumoniae meningitis. J Infect Dis. 2005; 191(5):783-90. [DOI:10.1086/427816] [PMID]

[10] Luo J, Song J, Zhang H, Zhang F, Liu H, Li L, et al. Melatonin mediated Foxp3-downregulation decreases cytokines production via the TLR2 and TLR4 pathways in H. pylori infected mice. Int Immunopharmacol. 2018; 64:116-22. [DOI:10.1016/j.intimp.2018.08.034] [PMID]

[11] Najafi F, Sarokhani D, Hasanpour Dehkordi A. The prevalence of kidney scarring due to urinary tract infection in Iranian children: A systematic review and meta-analysis. J Pediatr Urol. 2019; 15(4):300-8. [DOI:10.1016/j.jpurol.2019.05.011] [PMID]

[12] Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: Under promises but over delivers. J Pineal Res. 2016; 61(3):253-78. [DOI:10.1111/jpi.12360] [PMID]

[13] Taher A, Shokoohmand F, Abdoli E, Mohammadi Y, Mehrpooya M. A pilot study on the melatonin treatment in patients with early septic shock: Results of a single-center randomized controlled trial. Ir J Med Sci. 2022; 191(4):1913-24. [DOI:10.1007/s11845-021-02758-1] [PMID]

[14] Fathollahi A, Daneshgari F, Hanna-Mitchell AT. Melatonin and its role in lower urinary tract function: An article review. Curr Urol. 2015; 8(3):113-8. [DOI:10.1159/000365701] [PMID]

[15] Yao K, Zhang ZH, Liu MD, Niu FW, Li X, Ding DM, et al. Melatonin alleviates intrarenal CaOx crystals deposition through inhibiting LPS-induced non-canonical inflammasome-mediated renal tubular epithelial cells pyroptosis. Int Immunopharmacol. 2023; 124(Pt A):110796. [DOI:10.1016/j.intimp.2023.110796] [PMID]

[16] Drake MJ, Canham L, Cotterill N, Delgado D, Homewood J, Inglis K, et al. Results of a randomized, double blind, placebo controlled, crossover trial of melatonin for treatment of Nocturia in adults with multiple sclerosis (MeNiMS). BMC Neurol. 2018; 18(1):107. [DOI:10.1186/s12883-018-1114-4] [PMID]

[17] Leerasiri P, Pariyaeksut P, Hengrasmee P, Asumpinwong C. Effectiveness of melatonin for the treatment of nocturia: A randomized controlled trial. Int Urogynecol J. 2023; 34(2):485-92. [DOI:10.1007/s00192-022-05232-3] [PMID]

[18] Dipasquale V, Palermo L, Barbalace A, Tumminello G, Romano C. Randomised controlled trial of melatonin for paediatric functional abdominal pain disorders. J Paediatr Child Health. 2023; 59(3):458-63. [DOI:10.1111/jpc.16323] [PMID]