Survey on single dose Gentamicin in treatment of UTI in children from 1 month to 13 years in Jahrom during 2015

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Abstract

Introduction: After upper respiratory tract infection (URTI), the second cause of infections in children is urinary tract infections (UTI). About 3 to 5 percent of girls and 1 percent of boys have suffered from UTI. Gentamicin injection, three times a day is the treatment for UTI. One of the most serious problems of treatment with gentamicin is its multiple use and its associated complications. The aim of this study was evaluation of treatment of UTI with a single dose of gentamicin first as 3 mg / kg daily IV and after urine culture becomes negative on the second day of treatment 1mg / kg daily IM in children with from 1 month to 13 years in Jahrom during 2015.

Methods: This was a randomized clinical trial study performed on 64 children aged 1 month to 13 years who were randomly divided to case and control groups. All of the children had suffered from UTI. Urine culture was used for detection of pathogens. Data such as sex, age, fever, leukocytosis and treatment complications were gathered and analyzed. After treatment the patient was followed up for 6 weeks for detection of recurrence.

Results: Age: 78.12% of control of the case group and 87.5% of case group were under 6 years old. 68.75% of the control group and 75% of the case group were female. The prevalence of E.coli in the control group was 71.87% and in the case group was 75% which had the most prevalence in both groups. Response to the treatment in the control group was 93.75% and in the case group was 96.87%. Recurrence of disease in the control group was 28.14% and in the case group was 25%. Ototoxicity (decrease 15 db-) was not observed in patients, but data showed that 3.12% of control group suffered from nephrotoxicity(increased Cr twice) , although this percent was 0 in the case group. In regard to response to the treatment, recurrence of disease, and complications of treatment, no significant differences were observed (P>0.05).

Conclusions: Data showed no significant differences in response to the treatment and its complications between the two studied groups. Because of pain tolerance of injection and use of low dose, cost beneficence for parents and hospital, low use of syringe, lack of personnel and nurses, prevention of hospital admissions, and decreasing of complications associated with multiple use of gentamicin injection, it is recommended to use of single dose a gentamicin for treating UTI.

Key words: Urinary tract infection,
Single dose treatment, Gentamicin, E.coli.

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Introduction

Urinary tract infection (UTI) is the second most common cause of infection in children after upper respiratory tract infections [1], as it affects 3-5% of girls and 1% of boys [2]. The most common age of UTI is under 5 in girls and under 1 in uncircumcised boys [2]. The ratio of afflicted boys to afflicted girls is 2.5-8.4:1 in the first year of life and 10:1 after the age of one [2]. Its most prevalent pathogen in girls is E. coli (75-90%), followed by klesiella and then proteus, whereas proteus may be as common as E. coli in boys aged over 1 [2]. The key point in most cases of UTIs is timely diagnosis and proper treatment. In the current situation were resistant species of gram-negative bacteria are expanding, aminoglycosides, including gentamicin, are still considered among the strong and effective drugs for the treatment of UTIs [3]. It is noteworthy that the use of aminoglycosides can lead to nephrotoxicity and also auto toxicity (renal and hearing poisoning). Therefore, doctors try to reduce the odds of these poisonings by prescribing the right amount of medicines. Accordingly, they either increase the intervals between drug administrations or decrease their dosage [4]. Aminoglycosides are usually administered to children and infants two or three times a day. One of the major problems with taking these drugs is the frequency of injections which may cause problems such as pain tolerance (for children and infants) and a waste of time and money (for their parents) [5]. On the other hand, the reluctance of the patient or their parents to be hospitalized and lack of access to facilities make doctors apply outpatient treatments. In this case, fewer injections definitely further satisfy the patient and their parents. Recent studies in adults have shown that taking aminoglycosides once a day maximizes antibacterial activity and minimizes their toxicity [6, 7, 8]. However, a few studies have been conducted on children and infants in this regard and most of them have recommended further studies to be conducted on this population [9]. In a review of 24 studies about different aminoglycosides, it was concluded that although the use of aminoglycosides in a single dose is recommended in children, more studies are needed to prove its usefulness [10]. In another study on three comprehensive studies, it was recommended that although a single dose of aminoglycosides is useful in the treatment of UTIs, more studies should be conducted on children because patients are genetically different, they respond to the drug differently, and the dosage of medications varies from 3 to 7 mg per kilogram of body weight [11]. In other research conducted by Chong et al. in Singapore, 210 patients were studied in a randomized controlled trial. The patients, whose age ranged between one month and 13 years, were randomly divided into two groups. The first group received 5 mg of gentamicin per kilogram of body weight in a single dose and the second group was treated with 6 mg of gentamicin per kilogram of body weight in three days. Their results showed that there is no significant difference between the two groups in terms of treatment duration, medicine discontinuation at night, age, nephrotoxicity, and auto toxicity [6]. In a cohort study in 2011, 79 patients aged between one month and 16 years were divided into two groups and treated with 7 mg per kg of gentamicin in a single dose over three days. The results indicated that the single dose administration led to the non-prevalent and reversible nephrotoxicity and affliction of only one patient, and more prevalence of auto toxicity (2 patients were afflicted) [12]. In another study conducted in 2011 in Australia, 179 children aged between one month and 12 years were divided into two groups and treated with 5-7 mg per kg of gentamicin in a single dose and in three days. At the end of the trial, both groups responded to the treatment and no case of nephrotoxicity or auto toxicity was observed [5]. In another study, 49 children aged between 6 months and 12 years were randomly divided into two groups and treated with 4.5 mg per kg of gentamicin in a single dose and three doses. In the single dose group, the fever of patients was discontinued earlier and the result of the urine culture test was negative in patients of both groups in the first 48 hours. In the three doses group, nephrotoxicity was more prevalent and it was concluded that the single-dose administration of gentamicin is safer, more useful, and more economical [13]. Although UTI is the second most common cause of infection in children after upper respiratory tract infections [1], its prevalence is higher in children aged under 5 [2]. Multiple injections in a day may cause problems such as pain tolerance (for children and infants) and waste of time and money (for their parents) [5], and the single-dose administration is more appropriate in most cases. The effectiveness of this method should be proven by conducting more studies [11, 12, 13]. Several important differences were the trigger for the conducting of this study: a) genetic differences between patients [11], b) differences of patients in response to gentamicin in numerous studies [11], c) difference in the dose of gentamicin in various studies (4-7 mg per kg of body weight) [10, 11, 14], d) scarcity of studies on children unlike those conducted on adults [10, 11, 14], and e) gentamicin is usually administered to patients of the control and test groups at a concentration of 4-7 mg per kg of body weight in a single or multiple doses. In the present study, subjects of the control group intravenously (IV) received gentamicin at 3 mg per kg of body weight three times a day [2]. In the test group, the subjects were firstly treated with 3 mg gentamicin per kg of body weight in a single dose (IV) and then received it intramuscularly (IM) after a negative urine culture on the second or third day of treatment at 1 mg per kg of body weight. This indicates a significant difference between the present study and other previous ones in terms of dosage and injection method, because the subjects were studied in an outpatient manner rather than the inpatient manner after a negative urine culture.

Methods

This study was a clinical-controlled trial and according to previous studies, the sample size of 64 pediatric patients with UTIs admitted in the pediatric ward at Motahhari Hospital, selected by pediatric specialist diagnosis, were entered into the study. In the implementation of the project, the consent of the parents of the child was taken and the plan was implemented in compliance with all the ethical

regulations required in the research. The name and identity of the individuals remained confidential. No costs were received for urinalysis, audiometry and sonography examination. The criteria for entering the study included: children aged 1 month to 13 years with UTIs and exit criteria from the study included: age less than one month and over 13 years, renal failure before treatment, hearing impairment before starting treatment, taking Aminoglycoside before the onset of treatment, allergy to aminoglycosides, co-administration of another nephrotoxic drug, and urinary obstruction. Children admitted to the pediatric ward of Motahhari Hospital, who were admitted with UTI diagnosis of the pediatrician, were randomly divided into two groups of test and control, after permission from the parents of the patients. The criterion for diagnosis of UTI is positive urine culture which in case of using a urine bag, at least two positive identical urine culture with an organism of more than 105 colonies and, if using mid-urine culture sample, at least one positive cultures with an organism more than 105 and if using a catheter, the existence of at least 103 colonies of an organism was considered a UTI. At the time of sampling, all the necessary notes were given to the patient companion for a safe and sterile sampling (such as cleaning the urethra before sampling, closing the door of the sample vessels and quickly transferring to the laboratory, etc.). Samples were cultured in EMB and blood agar environments, and TSI, Citrate tests were used for diagnosis of bacteria.

The results of the samples were in three forms:
A. Examples which were negative and excluded.
B. Samples which were mixed growth, and were mixed growth after the repeat testing again, were discarded from the study.
C. Samples that were positive after 2 times urine culture, were included in the study.

Urine culture was also repeated 48 hours after treatment, and in the absence of negative culture after 48 hours of treatment, were considered as not responding to treatment and were excluded, and the treatment continued on the basis of standard treatment. At the end of the treatment, urine culture was repeated as well.

Before the start of the treatment, PTA auditory tests and kidney function tests (Bun, Cr) and electrolytes (Na, K) and CBC and sonography of the urinary tract were performed for all patients. In the case of abnormal kidney function tests and abnormal urinary tract sonography or the presence of abnormalities in the auditory system, the patients were excluded from the study. During and after treatment, renal function tests were performed which, when doubling, serum creatinine was considered as nephrotoxicity. At the end of the treatment, once again, the patient was tested for auditory examination, which was considered as an auto-toxicity in the case of a reduction of 15 dB S.N.HL. After the treatment, patients were followed up for 6 weeks, and again in case of having urine symptoms or any fever or illness, the urine culture was sent, and if the culture was positive, the same type of bacterium was considered as a relapse of the disease. The samples were collected and cultivated from the beginning of the year 2015 to the end of the year (March) and the type of bacterium causing infection was determined by microbiological methods. The data was analyzed by SPSS software version 11 after entering Excel.

Results

According to the results, 25 (78.12%) of the control group and 28 (87.5%) of the case group were in the age group of below than 6 years. In terms of diagnosis of UTI, E. coli formed the majority of responsible organisms in both groups (71.77% in the control group and 75% in the case group), and Proteus in the control group and Klebsiella in the case group were in the next order (Table 1). The most common finding in both groups was an increase in the number of white blood cells. Para clinical results showed that in the control group, 14 people (43.75%) in the case group, and 16 (50%) in the control group had leukocytosis more than 10000 (Table 2). In terms of the bacteriological response, 2 cases from the control group and 1 patient from the case group were resistant to treatment. In all 3 cases, the urinary culture was not negative after 48 hours. Comparison of the data showed that the response to treatment is more in the case group (OR = 0.48, P = 0.036) (Table 3). In both groups, 3 patients had creatinine increase, were this value exceeded basal levels only in one person (3.12%) from the control group, which was considered as nephrotoxicity. However, the post-treatment retest showed creatinine return to basal counts in all 6 cases, and none of the subjects in the case and control groups had a hearing loss greater than 15db, therefore auto toxicity was observed in none of the two groups (Table 4). Of the control group, 9 (28.12%) and 8 subjects (25%) from the case group experienced bacteriological recurrences in a 6-week follow-up (Table 5). Chi-square and Fisher exact tests did not show a significant difference between the two groups in terms of response to treatment and complications from treatment and illness relapse ($p > 0.05$).

Discussion

Several studies have been carried out on the use of gentamicin in the treatment of UTIs and other infections. Gentamicin is one of the bactericide antibiotics from the aminoglycoside group. This antibiotic is condensed in the kidney parenchyma, and its effects remain in the kidney and urine long after it is cleared from the serum. More than 25 different studies have been conducted on the use of effective values of gentamicin and the modification of how to use 3 times a day (15-16). These studies are both in adult UTIs and in UTIs in children, infants, hospitals, and others (17-19). It is very difficult to compare the results of studies with each other regarding single-dose therapy since the selection of patients in different studies has been carried out in different ways (20-21). Some studies have investigated the effect of single-dose therapy on the first UTI and some on frequent UTIs (22-25). Others have considered both upper and lower infections (26),

Table 1: Frequency distribution of urine culture results in case and control groups

P-value	Case		Control		
	Relative	Absolute	Relative	Absolute	Frequency / Bacterium
0.316	75%	24	71.87%	23	Escherichia coli
	9.37%	3	15.62%	5	Proteus
	12.5%	4	6.25%	2	Klebsiella
	3.12%	1	6.25%	2	Other cases
	100%	32	100%	32	Total

Table 2: Frequency distribution of leukocytosis in both case and control groups

OR	P-value	Case		Control			
		Relative	Absolute	Relative	Absolute	Frequency	Bacterium
1.28	0.616	50%	16	43.75%	14	Yes	Leukocytosis WBC > 10000
		50%	16	56.25%	18	No	

Table 3: Frequency distribution of response and non-response to treatment (negative urine culture after 48 hours of treatment)

OR	P-value	Case		Control			
		Relative	Absolute	Relative	Absolute	Frequency	Measured variable
0.48	0.036	3.12%	1	6.25%	2	No	Response to treatment
		96.87%	31	93.75%	30	Yes	

Table 4: Frequency distribution of treatment-related complications

OR	P-value	Case		Control			
		Relative	Absolute	Relative	Absolute	Frequency	Treatment complications
0.32	0.494	0	0	3.12%	1	Yes	Nephrotoxicity
		100%	32	96.88%	31	No	
1	0.506	0	0	0	0	Yes	Auto toxicity
		100%	32	100%	32	No	

Table 5: Frequency distribution of disease recurrence after 6 weeks

OR	P-value	Case		Control			
		Relative	Absolute	Relative	Absolute	Frequency	Measured variable
0.851	0.042	3.12%	8	28.12%	9	Yes	Disease recurrence
		96.87%	24	71.88%	23	No	

and in some other studies, the first infection and recurrent infections have been studied together (27-28). In one study, the radiological examination of the urinary system was part of the protocol, but people with an abnormal urinary system were not excluded (26). The results of this study and other studies have shown the good and successful effect of daily infusion, along with less renal and ear toxic effects. Due to the prolonged effects of gentamicin in urine and kidneys, and its bactericidal effects depending on concentration, some studies have shown that low and sequential concentrations produce adaptive resistance in germs and the use of higher concentrations at longer intervals produce higher concentrations in the urine and kidneys, and have better effects in eliminating the organism and reducing the chances of resistance (29, 16, and 30-31). Another important effect of this prescription is the reduction of patient and personnel costs (32). The results of this study showed that single-dose gentamicin treatment did not differ in terms of response to treatment and the complications of treatment and relapse of the disease by repeated dose therapy and could be used as a safe and cost-effective treatment. The response to treatment, which was defined as a culture being negative after 48 hours of onset of treatment, was found in 93.55% of the control group and 96.87% of the case group. Chi-square test did not show any significant difference (P = 0.5). These results are comparable to the results of Wigano, which has observed 100% and 99% in the two groups of treatment responses (33). The results of Caraptise also showed a 97% response in the case group and 98% in the control group (34). Keren's studies also showed a 100% improvement in microbiology in the daily single-dose group and 92% in the multiple daily dosing groups (35). Complications due to treatment including nephrotoxicity (duplication of creatinine) and auto toxicity (more than 15 dB of hearing loss) also did not show any difference between the case and control groups. Studies have shown that there are many consequences for treatment complications. One of the problems found in these patients was a 30% increase in baseline creatinine, which included 3 cases in each group, but only in one case in the control group of these 6 cases, the creatinine had a doubling in increase compared to baseline creatinine, and creatinine test repeat in each of the six cases reported returned to baseline values. Wigano reported creatinine increase in 3% of patients in both groups, and reported no auditory toxicity in patients of both groups, both of the results were consistent with the above study (33). Caraptise also observed this in less than 2% of patients (34). Other studies also had similar results (27 and 37). In a study by Chong on 210 patients aged between one month and 13 years, there was no difference in response to treatment and complications from treatment. The difference between the study by Chong and the above study was that in this study, auto toxicity was defined as a hearing loss of more than 30db. However, the results of this study did not differ from the present study and other studies that considered auto toxicity as a reduction of 15-20 db (37-41). In the Emma study, the results such as response to treatment and recurrence of disease and nephrotoxicity, were in agreement with the present study, but in the Emma study, the auto toxicity rate was higher in single dose patients, which was different from the above study (42). Another variable that was studied in the present study was the measurement of recurrence rate in a 6-week follow-up, which was defined as urine culture being positive again in this 6-week period and observed in 28.12% of the control group and in 25% of the case group. According to Kallenius studies, the success rate of single-dose treatment was 100% and the probability of returning in the follow-up of 8 weeks was 52%, which was not significantly different from the present study in terms of response to treatment, but in terms of relapse, the results of these two studies are different (23). According to Khan studies, the success rate of single-dose treatment was 100% and the likelihood of returning infection in a 12-week follow-up was 67%, which was consistent with the response to the treatment of above study. However, it was different with the above study in terms of illness return, which, of course, the reason for the difference could be explained by the fact that the cause of a large reversal of the disease in the Khan study was the examination of patients with recurrent UTIs (24). In a study by Wallen, which assessed a single-dose of aminoglycoside called amikacin on UTIs, the probability of success of a single-dose treatment was 92.3% and the infection return probability was 26%, which is far closer to the results of the above-mentioned study (43). The meta-analysis study carried out by Barza et al. in 1996 also confirms the results of the above study, and even this study indicates a low nephrotoxicity in the single-dose group, and therefore recommends single-dose treatment (44). In a study by Labovitz in 1972 with the aim of investigating the effect of a single dose of gentamicin on UTI, it was also stated that there was no statistically significant difference between the two treatment groups in terms of response to treatment. This study also confirms the results of the above study in terms of auto toxicity but the difference is that in this study, Gentamicin auditory complication has been investigated with vestibular function through clinical examination, which does not seem to be accurate (45). A study by Dr. Hossein Fallahzadeh et al. confirmed the above study in terms of response to treatment and relapse of the disease and nephrotoxicity, because there was no difference between the two treatment groups in this study (P <0.36). The difference between the two studies were that in the study of Dr. Fallahzadeh, the effects on hearing of gentamicin were not investigated (25). In a study conducted by Dr. Shams Vazirian et al., there was no significant difference between the two groups in terms of response to treatment, recurrence and Oscars (P<0.5). This study also agreed with the results of the study. The difference between the two studies were that in the above study, patients were not evaluated for Oscar creation, and Gentamicin's hearing impairment was not evaluated in Dr. Vazirian's study (46). In a study done by Dr. Shakiba et al. in 2000 on 82 patients, there was no difference in response to treatment and the complications of treatment between the two treatment groups. The difference was that in this study, the auto-toxicity was investigated only based on clinical symptoms indicating auditory complications, which were not sufficient (47). The results of the study done by Dr. Honarpisheh et al. in 2006 on 30 patients also agreed with the results of

the above studies regarding the response to treatment and nephrotoxicity, but the objection in this study was that the response to treatment was considered as the cessation of fever which did not seem to be adequate, and the other difference that this study had with the present study was that the hearing impairment of gentamicin was not studied (48). This study was in agreement with the study by Dr. Emam Ghoreishi et al regarding the response to treatment, but it was opposed for nephrotoxicity, because in the study of Emam Ghoreishi, the rate of nephrotoxicity was higher in the single dose group (49).

Conclusion

The final result is that there are no significant differences between the two standard treatment groups and once daily gentamicin treatment in terms of therapeutic response, renal and auditory complications, and recurrence of the disease, and this method can be used as a cost-effective, effective and low complication method.

Recommendations

It is suggested that interventional factors such as demographic information, mother's education, the economic, social and family background and the underlying illnesses of child and the status of the children immune system should be taken into account when conducting research on the treatment of UTIs in children.

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