Received: 25.1.2011 **Accepted: 2.4.2011**

Short Communication

Effect of hydrochlorothiazide on reducing recurrent abdominal pain in girls with idiopathic hypercalciuria

Parsa Yousefi[a], *Ali Cyrus*[b], *Fatemeh Dorreh*[a], *Nafiseh Gazerani*[c], *Hamid Reza Sedigh*[d]

Abstract

BACKGROUND: This study assessed the possible effect of hydrochlorothiazide (HCT) on soothing recurrent abdominal pain (RAP).

METHODS: A hundred girls with RAP and IH were randomly assigned into two groups of experiment (treated with hydrochlorothiazide 1mg/kg/day) and control and all patients were followed for 3 months.

RESULTS: In the experiment group, the mean of painful attacks in the first, second and third month were 0.38, 0.4 and 0.26, respectively which were far less than their counterparts in the control group.

CONCLUSIONS: Single daily dose of HCT is a safe and effective therapeutic option in the treatment of RAP in children with IH.

KEYWORDS: Recurrence, Abdominal Pain, Hypercalciuria, Hydrochlorothiazide, Child.

JRMS 2011; 16(Special Issue): 433-436

Recurrent abdominal pain (RAP) is one of the most common causes of referral to pediatric clinics. It usually induces anxiety in children and their parents, and is one of the challenging problems in pediatric medicine.[1] RAP is originally defined as a pain syndrome consisting of at least three episodes of abdominal pain over a period of 3 months or pain within one-month interval, severe enough to affect activities.[1,2] Location of pain depends on age; in children over 8 years old is more common in flank and in younger ones it is more diffuse or more centrally located.[3] To discover the etiology of these pains a wide range of procedures have been recommended with little diagnostic yields.[1,2] One of the causes of RAP is idiopathic hypercalciuria (IH), a common finding among children. It has 9% prevalence in normal children, but in those referred to nephrology clinics the prevalence is as high as 20%.[4,5] Nevertheless, IH has not been mentioned as a cause of RAP in reference books yet. Some recent studies with small sample sizes disclosed that IH could predispose patients to pain by inducing voiding dysfunction and tubular scraping secondary to oxalate calcium crystals.[6] In a study performed in 2001 by Vachvanichsanong et al, 41% of children with idiopathic hypercalciuria and no urolithiasis showed RAP. All children were treated with increased fluid intake and a reduction in dietary sodium and oxalate and some required treatment with thiazide and antispasmodics.[6] Regarding difficulties in prolonged dietary regimes and increased fluid intake in children,[7] it was decided to assess hydrochlorothiazide

[a] Assistant Professor, Department of Pediatrics, Arak University of Medical Science, Arak, Iran.
[b] Assistant Professor, Department of Urology, Arak University of Medical Science, Arak, Iran.
[c] MSc Student in Midwifery, Shahid Beheshti University of Medical Sciences, Arak, Iran.
[d] Specialist of Nuclear Medicine, Arak, Iran.
* Corresponding Author
E-mail: parsayousefichaijan@yahoo.com

(which is a safe and inexpensive diuretic with inhibitory effect on Na-Cl pomp in distal tubule) in the management of these patients.

Methods

In this single blind clinical trial, girls aged 5 to 12 years who referred to Amir Kabir hospital, Arak, Iran due to RAP with documented idiopathic hypercalciuria (24 hours urine calcium excretion greater than 4 mg/kg/d or random urine calcium-creatinine ratio greater than 0.25 mg/kg) were assessed and 100 girls who did not have UTI or any underlying abnormalities other than idiopathic hypercalciuria were selected. We only selected girls to unify gender of both intervention and control groups. Furthermore, UTI in boys with idiopathic hypercalciuria is usually accompanied by underlying and anatomical abnormalities.

Written consent was obtained from all parents after thorough explanation. Then a questionnaire was filled about the underlying diseases like constipation, voiding dysfunction, previous UTIs, parasitic infections, diabetes, urolithiasis and disorders that can cause secondary hypercalciuria such as ingestion of Vitamin D, supplementary calcium, hypothyroidism and RTA. A meticulous clinical examination and necessary lab tests were done. Besides all previous lab tests, radiographic and sonographic reports and hypercalciuria severity (urinary Ca/Cr ration) were registered in the checklist. A UA/UC test was taken from all patients at presentation to rule out UTI. All children with normal PTH, P and Ca, BUN and Cr, UA/UC and normal sonography with no secondary etiologies to explain their abdominal pain were recruited and assigned by simple randomization into intervention and control groups (50 in each group). In the control group, parents were instructed to assure adequate fluid intake and avoid salt consumption. In the intervention group in addition to aforementioned instructions, hydrochlorothiazide 1mg/kg/day by a single morning dose was administered.

For a period of three months after the initiation of the dietary regimen in the control group and normalization of urinary Ca/Cr ratio (below 0.25) after hydrochlorothiazide prescription in the other group, children were monthly visited by an authorized intern (who was not informed about the therapeutic intervention) to assess the frequency of painful attacks and assure dietary instructions and fluid intake as well as monitoring any signs and symptoms indicative of hydrochlorothiazide side-effect. Those with suspicious complaints were referred to a pediatrician.

UA/UC, serum Na/K (regarding HCT side effects) and urinary random calcium/ creatinine ratio were also checked on monthly basis. If there was no decrease in hypercalciuria to less than 0.25 in the first month, HCT was increased to 1.5 mg/kg/day and the next month Urinary calcium/creatinine ratio was checked again; if normal urinary calcium levels was confirmed, an additional 3 months follow-up was pursued.

Patients absent at follow up visits, non-compliant in drug consumption, those with non-cooperative parents, children on HCT who did not become normocalciuric despite 1.5 mg/kg/day of HCT, patients developing UTIs, those with side effects of HCT consumption and those developing hypotension secondary to drug consumption were excluded and replaced by similar cases.

The data on the frequency of painful episodes in both groups were analyzed by t-test. The Ethics Committee of Arak University of Medical Sciences observed ethics.

Results

In this study, 50 children were registered in intervention (HCT) group with an average age of 7.3 ± 2.06 and 50 patients were assigned in the control group (only dietary instructions) with an average of 7.8 ± 2.29, which were not significantly different. The youngest girl was 5 years old and the oldest one was 12 years old.

In the control group 78% in the first month, 84% in the second month and 94% in the third month experienced pain and in children who underwent HCT therapy the figures were 38%, 36% and 26%, respectively. The number of

Table 1. Comparison between number of painful episodes in terms of month in the intervention and control groups

Months	Case group (with hydrochlorothiazide)		Control group (no hydrochlorothiazide)		P value
	Average of pain attacks	Standard deviation	Average of pain attacks	Standard deviation	
First	0.38	0.49	1.60	1.19	< 0.001
Second	0.4	0.57	1.94	1.21	< 0.001
Third	0.26	0.44	1.84	0.97	< 0.001

pain episodes in the first, second and third months in the two groups is cited in table 1 while table 2 compares the average of pain bouts in three months, which discloses significant differences. The mean number of pain episodes during the three months was 0.3 and 12.33 in HCT and control children, respectively.

Discussion

RAP is a common problem in children and not only torments the affected children and their parents, but also sometimes leads to unnecessary and invasive procedures such as unnecessary appendectomies.[8]

In this paper, the effect of single dose of 1 mg/kg/day HCT on the abdominal pain in children with idiopathic hypercalciuria was studied. In the first month, 78% of children in the control group and 38% in the HCT group complained of abdominal pain. By the third month, 74% of children in the HCT group were free of pain while this figure was only 6% in controls. In a study by Penido et al on 417 children with IH, on follow up without therapy 64% continued to have RAP which was similar to the present study.[4] Vachvanichsanong et al got an 86% response rate to a combination of strict dietary restrictions and in a few cases addition of drugs.[6] Although our dietary restrictions were much looser, we had better results that could be attributed to HCT and probable noncompliance in some of Vachvanichsanong's patients. Vachvanichsanong et al did not compare children receiving HCT with those who were managed by dietary intervention alone. Polito et al had comparable results and nine out of eleven patients responded to the combination therapy.[8] However, the number of RAP patients in his study was too small to compare the results of dietary restrictions to HCT. Polito et al reported that 72% of his cases had no hematuria in the initial study and only 55% had previous episodes of dysuria.[9] These findings underline the need for vigorous search of IH in all children with RAP disregarding the absence of acompanied hematuria or dysuria.

The results of the present study revealed that compared to moderate dietary restrictions alone, consumption of HCT for more than 2 months had a more considerable effect on reduction of abdominal pain, accompanied with eradication of pain in many instances. Maintenance of strict dietary modifications in children is a challenge and HCT can definitely assist their management with a much looser diet.

Table 2. Comparison between number of pain attacks in three months of observation in the two groups of the study

	Control group (no hydrochlorothiazide)			Case group (with hydrochlorothiazide)		
Pain episodes	1st month	2nd month	3rd month	1st month	2nd month	3rd month
No pain	62%	64%	74%	22%	16%	6%
One	38%	32%	26%	26%	20%	24%
Two	-	4%	-	28%	26%	34%
Three	-	-	-	18%	30%	22%
Four	-	-	-	6%	8%	4%

No HCT induced side effects were noticed among children during the study and no one were excluded due to intolerance to HCT.

The present study was single blind and suffered from lack of placebo in the control group. Subsequently, further studies with RCT structures are crucial to confirm the results.

Conclusions

Since strict dietary restrictions and high fluid intake in children are not convenient, according to our findings, it seems that HCT, as a safe and inexpensive drug can be effective in ameliorating RAP is children with idiopathic hypercalciuria.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

PY developed and wrote the protocol and was responsible for the reference searching, data extraction, data analysis and interpretation of results. AC assisted in interpretation of results. FD assisted in data extract and interpretation of results. NG helped in reference searching, data analysis, interpretation of results and writing the manuscript. HS assessed the risk of bias in included studies, participated in interpretation of results and editing of the manuscript. All authors have read and approved the content of the manuscript.

References

1. Subcommittee on Chronic Abdominal Pain. Chronic abdominal pain in children. AAP news 2005; 115(3): 812-5.
2. Wyllie R, Tinanoff N, Orenstein S. The digestive system. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. 17th ed. Philadelphia: Saunders; 2003. p. 1197-356.
3. Polito C, Cioce F, Signoriello G, La Manna A. Central/diffuse abdominal perception of urological pain in children. Acta Paediatr 2006; 95(1): 82-5.
4. Penido MG, Diniz JS, Moreira ML, Tupinambá AL, França A, Andrade BH, et al. Idiopathic hypercalciuria: presentation of 471 cases. J Pediatr (Rio J) 2001; 77(2): 101-4. (Portuguese).
5. Polito C, La Manna A, Cioce F, Villani J, Nappi B, Di Toro R. Clinical presentation and natural course of idiopathic hypercalciuria in children. Pediatr Nephrol 2000; 15(3-4): 211-4.
6. Vachvanichsanong P, Malagon M, Moore ES. Recurrent abdominal and flank pain in children with idiopathic hypercalciuria. Acta Paediatr 2001; 90(6): 643-8.
7. Jackson EK. Diuretics. In: Parker K, editor. Goodman & Gilman's the Pharmacological basis of therapeutics. 11th ed. Boston: McGraw-Hill Professional; 2005. p. 753-89.
8. Polito C, Marte A, La Manna A. Appendectomy in children with hypercalciuria/hyperuricosuria. J Pediatr Urol 2005; 1(4): 279-82.
9. Yousefi P, Cyrus A, Dorreh F, Rashidi SM. The effectiveness of hydrochlorothiazide on preventing recurrent urinary tract infection in idiopathic hypercalciuric children. Arak Medical University Journal 2006; 9(2): 68-75. (Persian).