A Comparative Study Between Imipramine , Oxybutynin and Non Drug Therapy in Treating Nocturnal Enuresis

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ABSTRACT:

BACKGROUND:

Treatment with tricyclic antidepressants agents is the mainly used therapy for nocturnal enuresis also there are other agents such as anticholinergic drugs and desmopressin (nasal spray and oral) which are used to lesser extent also other modalities are used such as behavior modification.

OBJECTIVE:

We prospectively evaluated the effect of imipramine for treating children with nocturnal enuresis compared to oxybutynin and to non drug treatment.

METHODS:

We enrolled 149 patients of the age group more than 5 years from September 2006 to end of July 2007. The children were randomly assigned into three groups; the first (60 patients) treated with imipramine, the second (60 patients) treated with oxybutynin and the third (29 patients) treated with non drug therapy and the three groups were followed for more than 3 months. Treatment response was measured monthly for 3-6 months in terms of frequency of enuresis, tolerance to drugs and side effects of the drugs used . The recurrence of enuresis after stopping the treatment was also reported.

RESULT:

Of the 149 children followed 96(64.45%) were boys and 53(35.55%) were girls with 1.8:1 male to female ratio. Of those treated with imipramine 32 (53.34%) have complete dryness and 16 (26.66%) improved; while those treated with oxybutynin20 (33.3%) were dry and 20 (33.3%) improved. For those with non drug treatment 5 (17.2%) dry 14 (48.3%) improved and 10(34.5%) with no response.

CONCLUSION:

Treatment of nocturnal enuresis in children with imipramine was well tolerated and gave significantly faster and more cost-effective results than oxybutynin or non drug treatment, females had a significantly better response ($P<0.05$) than males in general.

KEY WARDS: nocturnal enuresis, imipramine and oxybutynin.

INTRODUCTION:

Enuresis is defined as involuntary voiding; when it occurs at night it is termed nocturnal enuresis and day time incontinence is termed diurnal enuresis. Because urinary incontinence occurs normally in infants and young children, its significance dependent on the age of the patient, parental expectations, and social and cultural factors . Approximately 15% of children still wet at night at age of 5 years. It is either primary when the child have never been dry, or secondary enuresis when the child has relapsed after initial night time dryness [1] .The male to female ratio for nocturnal enuresis is three to two [2] .It occurs more in children with positive family history (77% if both parents and 43% if single parent had the condition)[1, 3] . A carefully obtained history, physical examination and urinalysis are sufficient for evaluation of most children in order to exclude any underlying pathology (developmental, neurological, obstructive sleep apnea or organic urinary tract diseases) that might present with enuresis [1]. Treatment is not recommended before the age of 5 years because at this age only 15% of children are still wetting, and most urinary incontinence fades away naturally [4]. Treatment includes;

1-Non specific measures such as decrease fluid intake at night, awakening the child during night and avoiding specific food and drink,

2-Drug therapy which includes; tricyclic antidepressant (imipramine tablet), vasopressin analog (desmopressin) and anticholinergic drugs (oxybutynin tablets).

3-Behavior modification: recent studies, even in a limited number of cases, suggest the efficacy of behavioral therapy for enuresis [5].

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PATIENTS AND METHODS:

A randomized prospective study included 149 patients of the urology and surgery department in Al-Sader teaching hospital in Al-Najaf district, from the age group that is above 5 years of both sexes who complained of nocturnal enuresis. The study started from September 2006 to end of July 2007 for a period of 11 months and we studied the patients name, age, sex, residence, phone number, family history of nocturnal enuresis and sleep pattern (deep sleepers). History of neurological disorders (e.g. Back trauma, spinal cord lesion) , congenital abnormalities such as (spina bifida, hairy patches and back lumps) and history of urinary tract infection (all those patients who were with underlying pathology were excluded from the study and they were 25 patients) . Assessment depends on history of the condition, physical examination for both urological and neurological abnormalities and general urinary examination. The study population consisted of 174 patients but 25 were excluded so the remaining patients were 149 (53 girls and 96 boys) who wet the bed at least 7 nights in 2 weeks. After dividing them randomly into 3 groups; the first group (60 patients) treated with imipramine (Tofranil®) 25 mg for patients younger than 8 years and 50mg for older patients[6] , as a single dose at night shortly before bedtime the second group (60 patients) treated with oxybutynin (Ditropan ®) 2.5 mg for patients younger than 8 years and 5 mg for older patients[5] shortly before bedtime and the third group (29 patients) treated with non drug therapy which was consisted of measures such as restriction of fluid intake at night and avoidance of certain citrus fruits ,tea , coffee chocolate and cacao. All of the 3 groups treated for 3-6 successive months with monthly visit or phone call to check the condition of the patient and questions about bed wetting, tolerance to the drugs, adverse events and favorable effect were specifically asked .Children were considered full responders when the family stated that 0 to 1 wet night occurred in 2 weeks during treatment, intermediate responders if the reduction of the number of wet nights was more than 50%, and non responders if the drug has little or no effect [7]. Those patients are classified according to Gepertz into 3 age groups [7], 5 to 8 years,8 to 12 years and more than 12 years of age. Then we look for the following findings 1-Response to treatment; whether complete dryness, improved or no response. 2- Complications of the drugs. 3- The patient compliance. 4- Relapse of enuresis after cessation of treatment.

RESULTS:

Of the 149 patients studied 96 (64.45%) were males and 53 (35.55%) were females with a male to female ratio of 1.8:1 (table- 1). Those with primary nocturnal enuresis were 124 (83.3%) and 25(16.6%) were with secondary nocturnal enuresis. The highest cases reported were in the age group of 8 – 12 years of age which were 76 patients (51%) of which 52 were males and 24 were females and the lowest group affected was those above 12 years (13.4%) as shown in table 1. Patients with positive (+ve) family history were 89 (59.8%) and those with negative (-ve) family history were 60(40.2%) (Table 2).

The first group (those who were treated with imipramine), 32patients (53.4%) fully responded to treatment , 16 patients (26.6%) were with intermediate response and 12 patients (20 %) considered unresponders (table 3) .Side effects were encountered in 20 patients (33.3%) ; all of them were tolerable and there was no need to stop the treatment . Sleep disturbance was the commonest reported side effect (16.6%) followed by constipation and drowsiness (13.3% each), mood changes, dry mouth and difficulty of voiding as shown in table 7. In the oxybutynin treated group , the good response rate represented 33.3% (20 patients) which was similar to the intermediate response group and those who were unresponders (table 4).The side effects reported in 32 patients (53.34 %) and they included in decreasing order ; dry mouth , constipation , flushing and difficulty of voiding (table 7). The third (non drug treatment) group consisted of 19 males and 10 females , 5 of them (17.2%) responded well to the given instructions , 14 (48.3%) intermediately responded and 10 (34.5%) showed no response as shown in table 5 .Of course there were no side effects reported in this group . The over all response to treatment is more in female than male patients where it was 41.5% in females and 37.5 in males (p value < 0.5) as shown in table 6. Total side effect +ve patients were 52 (34.9%), 32 patients reported in the oxybutynin group representing 53.3% of that group and 20 patients (33.3%) of imipramine treated group. The total reported side effects were 98 that is to say more than one side effect had been reported in some patients as shown in table 7. Favorable side effects of imipramine were seen in 8(26.6%) children, who all became more calm and focused. The total cost of full course of imipramine (3 months) in our study was 1.5$ for single tablet patients and 3 $ for those 2 tablet patients, while in patients taking oxybutynin the total cost of full

coarse (3 months) was 7.5$ for 2.5 mg (1/2 tablet daily) patients and 15$ for 5 mg (one tablet daily) . The early relapse of nocturnal enuresis was also assessed by using the phone for a minimum of one month (for those who present late in the study) up to 3 months after stopping the treatment and it was highest in the non drug treated group (73.6%) followed by imipramine treated group (45.8%) and it was least in oxybutynin treated group (42.5%) as shown in table-8.

Table 1: Age and sex distribution of 149 children with nocturnal enuresis

Age/year	male	%	female	%	total	%
5-≤8	33	22.2	20	13.4	53	35.6
8-12	53	35.55	23	15.45	76	51
≥ 12	10	6.7	10	6.7	20	13.4
Total	96	64.45	53	35.55	149	100

Table 2: The relation between family history and nocturnal enuresis according to age group

Age/year	Positive family history	Negative family history	Total
5-≤8	23 (15.4%)	30(20.1%)	53(35.5%)
8-12	56(37.7%)	20(13.4%)	76(51.1%)
≥ 12	10(6.7%)	10(6.7%)	20(13.4%)
Total	89(59.8)	60(40.2%)	149(100%)

Table 3: The results of using of imipramine in 60 patients

age /year	Complete dryness (%)	Improved (%)	No improvement (%)	Total (%)
5-≤8	12 (20%)	4 (6.6%)	0	16(26.6%)
8-12	16(26.6%)	8(13.3%)	12(20%)	36(60%)
≥ 12	4(6.6%)	4(6.6%)	0	8(13.3%)
Total	32(53.3%)	16(26.6%)	12(20%)	60(100%)

Table 4: The results of using oxybutynin in 60 patients

Age/year	Complete dryness (%)	Improved (%)	No improvement (%)	Total (%)
5-≤8	12 (20%)	4(6.6%)	4(6.6%)	20(33.3%)
8-12	4(6.6%)	12 (20%)	12 (20%)	28(46.6%)
≥ 12	4(6.6%)	4(6.6%)	4(6.6%)	12 (20%)
Total	20(33.3%)	20(33.3%)	20(33.3%)	60(100%)

Table 5: The results of non drug treatment in 29 patients

Age/year	Complete dryness (%)	Improved (%)	No improvement (%)	Total (%)
5-≤8	0	6(20.7%)	8(27.6%)	14(48.3)
8-12	3(10.3%)	8(27.6%)	2(6.9%)	13(44.8%)
≥ 12	2(6.9)	0	0	2(6.9%)
Total	5(17.2%)	14(48.3)	10(34.5%)	29(100%)

Table 6: The response to treatment according to gender

Age/year	Imipramine		Oxybutynin		Non drug		Total (%)	
	Male %	Female%	Male %	Female	Male%	Female%	Male%	Female%
Complete dryness	20 (20.8%)	12 (22.6%)	12 (12.5%)	8 (15.1%)	4 (4.16%)	2 (3.7%)	36 (37.5%)	22 (41.5%)
Improved	8 (8.33%)	8 (15.1%)	16 (16.6%)	4 (7.5%)	8 (8.33%)	5 (9.4%)	32 (33.3%)	17 (32.1)
No improvement	12 (12.5%)	0	8 (8.33%)	12 (22.6%)	8 (8.33%)	2 (3.7%)	28 (29.1%)	14 (26.4%)
Total	40 (41.6%)	20 (37.7%)	36 (37.5%)	24 (45.3%)	20 (20.8%)	9 (16.9%)	96 (100%)	53 (100%)

Table 7: Side effects of drugs according to gender

Complication	Imipramine		Oxybutynin	
	male	female	male	female
Drowsiness	8(13.3%)	0	0	0
Sleep disturbance	10(16.6%)	0	0	0
Constipation	8(13.3%)	0	14(23.3%)	4(6.6%)
Dry mouth	2(3.3%)	4(6.6%)	14(23.3%)	8(13.3%)
Flushing	0	0	4(6.6%)	8(13.3%)
Mood changes	2(3.3%)	4(6.6%)	0	0
Voiding difficulty	2(3.3%)	2(3.3%)	2(3.3%)	2(3.3%)

Table 8: The relapse of nocturnal enuresis after finishing the courses of treatment

Age/year	Imipramine*	Oxybutynin *	Non-drug*
5- ≤8	10(20.8%)	8(20%)	6(31.5%)
8 -12	9(18.75%)	6(15%)	8(42.1%)
≥12	3(6.26%)	3(7.5%)	0
Total	22(45.8%)	17(42.5%)	14(73.6%)

- The percent represent the percentage of the number to the summation of both fully responded group and those with intermediate response group (tables 3, 4 and5).
- P value > 0.05

DISCUSSION:

The major limitations of our work were the difficulty with the follow up of the patients because it was done, for most of the time by the use of the phone; the other difficulty was the unavailability of the drugs which occurred sometimes in our hospitals (due to defect in supply).

It is mentioned that only 15% of enuretics have an initial dry period [8, 9] which is close to our result (16.6%) of secondary enuresis which may resulted from the development of stressful conditions. There is a significant sex distribution in nocturnal enuresis were it is 50% more common in boys than girls (1,8) ; in the present study males represent 64.4% and females 35.6% with a ratio of 1.8:1which is slightly higher than the reported ratios in the fore mentioned studies which might be in part due to the neglection of the condition in females from the parents side and social background of our society .

Full response to treatment was significantly better in females(41.5%) than males (37.5%) (P<0.05) which

was in accord of other studies (4, 10) with unknown explanation .Heredity plays a significant contributing factor in the etiology of nocturnal enuresis [4, 11], which was also obvious in our study where 59.8% of enuretics had a positive family history of the condition (P<0.05). Gepertz and Neveus (2004)[7] state that 50% of enuretic children respond favorably to imipramine treatment , which was near to our result 53.3% .

The response to oxybutynin was 33.3% which was also associated with higher rate of side effects than imipramine treated group (53.3% vs 33.3%) which indicates the relative safety of imipramine in this study despite the reported cases of sudden death and cardiac arrythmias[7,12] which was not seen in this study and might be dose related .

In our study we noticed that the most affected age group was 8 - 12 years (51.1%) which mean that the parent begin to be anxious about the symptom and consult the doctor for it at the school age while in Wile study [13](in Baghdad city) 60% of children affected were below 8 years of age .

The rate of early relapse in imipramine treated group was 45% which is in the range of what was reported by Stephen [1] and Cendron[14] (50%) while that of oxybutynin treated group was 42% which is slightly lower than that of imipramine group but the response rate was higher in the later group (53.3% vs 33.3%) making imipramine a better option . We also compared the cost of treatment in our study which was less costly in imipramine than oxybutynin compared to generic world prices.

CONCLUSION:

Imipramine is more useful for the treatment of nocturnal enuresis in comparison to oxybutynin and non drug therapy, have less side effects and more patient compliance and less costly.

Our article is not to be taken as a general recommendation to increase the use of imipramine, but as an argument that the drug still the first line in the treatment of enuresis in the absence of other more safe and successful modalities such as retention control training, responsibility re-enforcement and conditioning therapy by urinary alarm apparatus which is considered as the most effective approach for nocturnal enuresis.

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