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Comparative efficacy of Imipramine, Oxybutinin, and Desmopressin in managing children with primary nocturnal enuresis

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ABSTRACT

To study the comparative efficacy of Imipramine, Oxybutinin and Desmopressin in managing children with primary nocturnal enuresis. The present study was carried out on 90 children of either sex presenting with the criteria of primary nocturnal enuresis. Study subjects were randomly divided into three groups of 30 children- Imipramine group (Group I), Oxybutinin group (Group II) and Desmopressin group (Group III). Following variables were compared: night time bladder control , number of dry nights, compliance, side effects and relapses during follow-up. Difference in intergroup drug compliance was not significant indicating that all the 3 drugs regimen were well adhered. In group I, 20% of the cases showed adverse effects. In group II and III the corresponding figure was 16.7%. Cases responding to the drug treatment were 43.3% in Group I, 30 % in group II and 70% in group III respectively. Among 13 responders in group I; 10 (76.9%) relapsed at the end of follow up period. Of 9 responders in group II; 3 (33.3%) relapsed and among 21 responders in group III; 7 (33.3%) relapsed. It is concluded that all the three drugs cause significant reduction in wet nights. However Desmopressin had the highest response rate and the lowest relapse rate. Imipramine had a better response rate than Oxybutinin but it also had the highest relapse rate among the three drugs. All the 3 drugs had minimal side effects, hence the compliance was very good in all the 3 groups.

INTRODUCTION

Nocturnal enuresis (NE) denotes bedwetting or sleep wetting only [1]. Incontinence is normal, nearly complete evacuation of bladder but at the wrong place and wrong time, at least twice a month after 5 years of age [2]. Nearly 85% of children usually have normal complete bladder control by 5 years of age. Primary nocturnal enuresis is involuntary voiding of urine during sleep in healthy children >5 years of age for >2 nights per week for >14 nights per month. Approximately 25%-30% of children with bed wetting are secondary enuretics who achieve a dry interval of at least 6 months and then revert back to bed wetting [3]. Three pharmaceutical agents are commonly used in the management of nocturnal enuresis; Imipramine, Oxybutinin and Desmopressin (DDAVP)[4].

MATERIAL & METHODS

The study was carried out on 90 children of either sex presenting with the criteria of primary nocturnal enuresis in the outpatient department. It was a prospective type of study design. A written informed consent was taken from all the patients. Study subjects were randomly divided into three groups of 30 children each depending on the choice of drug used:- Imipramine group (Group I),Oxybutinin group (Group II) and Desmopressin group (Group III).

Children >5 years of age with involuntary voiding of urine during sleep in healthy children for >2 nights per week for >14 nights per month [2] and not manageable by psychotherapy or behavioral modification were included in the study. Children <5 years of age or having secondary nocturnal enuresis or who had already taken any form of pharmacotherapy or with obvious spinal or neural anomalies or with any one or combination of the following:-urinary tract infection, chronic renal failure, diabetes insipidus, diabetes mellitus, urogenital anomaly, urinary tract surgery were excluded from the study.

Compliance was defined as children taking the respective drug for at least 80% of the total duration. Continence was zero to

one enuretic night monthly. Relapse was defined as three or more wet nights during a period of 14 consecutive nights following the successful completion of treatment.

Detailed history was taken to know the pattern of enuresis (day, night, frequency, duration), any associated urgency and frequency of urination, presence or absence of fecal soiling, behavioral or learning problems, age of toilet training, any voiding difficulties, family history, presence of any stress, socio-economic status and previous attempts at treatment. A questionnaire in local language was prepared to elicit accurate history.

The physical examination included detailed general physical examination and a careful evaluation of the respiratory, cardiovascular and nervous system along with the examination of the abdomen, spine and external genitalia. Laboratory investigations included total red cell count, total and differential white blood cell count, blood urea, blood sugar, serum sodium and potassium, serum creatinine, complete urine examination, urine culture and sensitivity, stool microscopic examination and ultrasound of the abdomen.

The parents were instructed to keep records of nocturnal bed wetting episodes and note adverse effects if any. Imipramine was prescribed at a dose of 0.9-1.5mg/kg/day orally, Oxybutinin at 0.2mg/kg/day at bedtime orally and Desmopressin at 10-40µg/day at bed time as nasal inhalation. After start of drug therapy, first clinical assessment was made after 8 weeks in case of Imipramine and Oxybutinin groups and after 12 weeks in case of Desmopressin group. It was followed by 2 weekly follow up for a total duration of 6 months. Attaining night time bladder control and number of dry nights, compliance, side effects and relapses during follow-up were compared within the group and among all the 3 groups. The results were statistically compared using student t- test (paired and unpaired) and further analyzed.

RESULTS

Of the 30 children in each group the mean age of group I was 8.971.99 years, mean age of group II was 8.32.15 years and mean age of group III was 8.52.3 years. The sex distribution in the 3 groups was as follows: Group I: 70% males and 30% females; Group II: 46.7% males and 53.3% females; Group III 50% males and 50% females. The mean age of toilet training of cases of group I was 2.080.32 years, in group II was 2.100.44 years and in group III was 2.100.46 years. Of the total cases in group I; 33.3% had associated features and 16.7% of cases had behavioural problem. In group II 40% of cases had associated features and 13.3% had behavioural problems. In group III 16.7% of the cases has associated features and 20% had behavioural problems. Of 30 cases in group I, 5 cases (16.7%) had familial history of NE and none had any history of family stress. In group II; 10 cases (33.3%) had history of NE in family and 2 cases (6.7%) had positive history of family stress. In group III, 16.7% of the cases had a history of similar illness in the family and 10% of the cases had family stress in the family. In group I the cases had on average 24.44.62 wet nights per month and 2.23±1.07 enuretic episodes per night before treatment. In group II the corresponding values were 24.05.94 wet nights per month and 2.20.92 enuretic episodes per night. In group III the cases had a mean of 24.14.51 wet nights per month and 2.31.16 enuretic episodes per night. The cases were matched with respect to all of the above factors.

Among 30 cases in group I, 96.7% of the cases had good drug compliance. In group II all the cases were compliant. In group III, 93.3% of the cases showed good drug compliance. Intergroup drug compliance difference was not significant indicating that the entire 3 drugs regimen were well adhered to. In group I, 20% of the cases showed adverse effects. In group II and III the corresponding figure was 16.7%. In group I the mean reduction in wet nights per month at the end of drug administration period was 22.634.61 i.e. from 24.44.62 to 1.771.22. This difference was statistically very significant ($p<0.001$) indicating response to the drug. In group II the incidence of wet nights per month decreased from 24.05.94 to 1.81.06 with a mean reduction of 22.226.35 wet nights per month which is statistically very significant ($p<0.001$). In group III statistically very high response to the drug is indicated by reduction in wet nights from 24.14.51 per month before treatment to 1.11.21 per month after treatment with a mean reduction of 23.04.59 wet nights per month ($p<0.001$). [Fig.1].

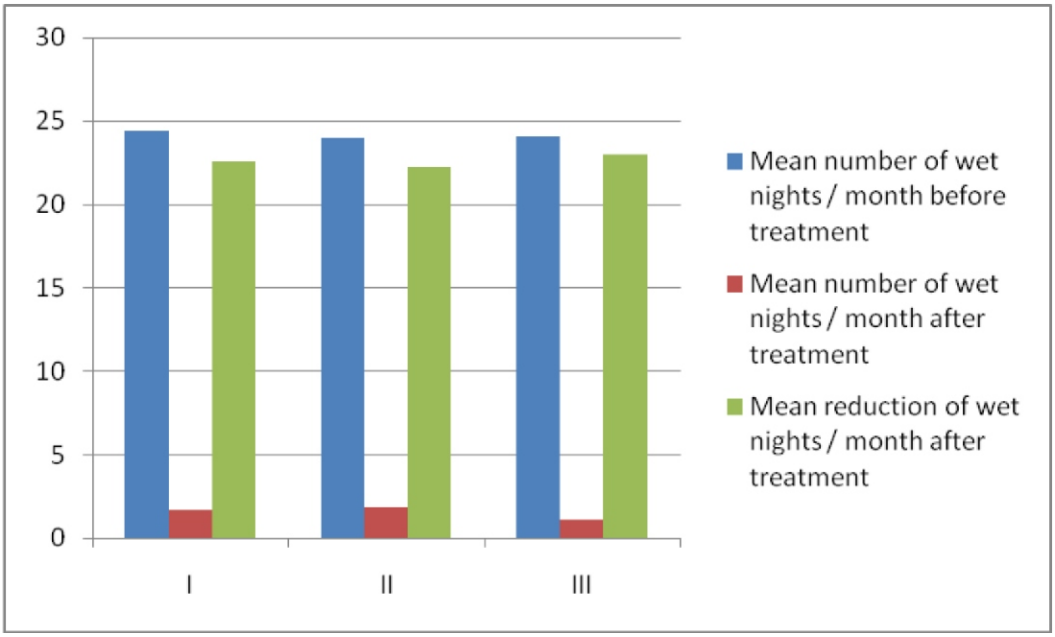

Fig. 1. Impact of Treatment on Wet Nights

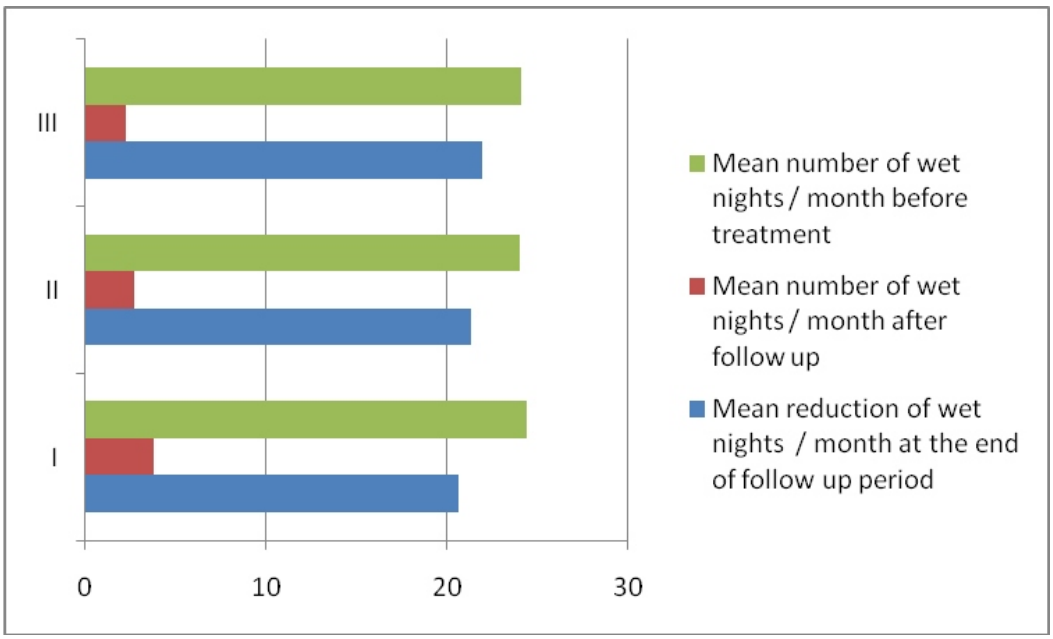

Fig. 2. Long Term Impact of Treatment on Wet Nights

Group I had 43.3% of the cases who responded to the drug treatment. In group II, 30% of the cases responded to the drug treatment. However 70% of group III cases responded to the drug treatment. Although the intergroup comparison of mean reduction of wet nights per month does not show any statistically different value but difference of mean number of wet nights between group I and group III and also between group II and group III was statistically significant, indicating better response with Desmopressin in net reduction of wet nights. A comparison of change in mean number of wet nights per month from the end of drug administration period to the end of follow up period shows group I had change from1.771.22 wet nights per month to 3.81.71 wet nights per month, group II had change from 1.81.06 to 2.671.67 wet nights per month and group III had change from 1.11.21 to 2.21.9 wet nights per month. All the above 3 results are statistically significant ($p<0.001$). Among 13 responders in group I; 10 (76.9%) relapsed at the end of follow up period. Of 9 responders in group II; 3 (33.3%) relapsed and among 21 responders in group III; 7 (33.3%) relapsed.

The mean number of wet nights per month at the end of study in group I was 3.81.71. It was 2.671.67 wet nights per month in group II and 2.21.9 wet nights per month in group III cases. There was statistically significant difference between group I and group II and also between group I and group III. However the difference was not statistically significant between group II and group III. [Fig.2]

DISCUSSION

Nocturnal Enuresis (NE) occupies considerable time in the general pediatric practice and is often accompanied by major psychosocial issues. It is just one of the various forms of urinary incontinence. In the present study, 16.7% of cases in group I, 13.3% in group II and 20% of cases in group III had behavioural problems ranging from increased irritability to shyness and forgetfulness. Hjalmas et al (2004) had reported that 13.5% to 40.1% of all wetting children have clinically relevant behavioural problem [1].

Group I had 43.3% of the cases who responded to pharmacotherapy. In group I there were 13 continent cases at the start of follow up period which got reduced to 3 at the end of follow up period. Large number of placebo controlled study has shown that about 50% of enuretic children were cured by Imipramine [5]. Wagner et al (1982) enrolled 49 patients in a study and found that 33% of cases receiving Imipramine responded compared to 83% responders in conditioning program group and 81% responders in waiting list group [6]. Shaffer et al (1968) while studying 62 enuretic school children found 20 of 56 children to be continent while receiving Imipramine [7]. In the study by Kunin et al (1970), cases treated with Imipramine showed 51.4% decrease in enuresis ($p<0.01$) [8]. Among 44 patients, studied by Monda and Husmann (1995), 36% of patients became dry while on medication with $p<0.01$ as compared to observation alone [9].

Imipramine might decrease enuresis by reducing detrusor activity, increasing bladder capacity and by not allowing the nocturnal increase in intravescical pressure which occurs in stages III and IV of sleep. Also Imipramine decreases the frequency of lightening of the EEG sleep pattern which constitutes the enuretic episode. Hence the efficacy of Imipramine in reducing the episodes of NE [10].The treatment of enuresis with Imipramine appears to be correlated with the serum level of Imipramine. Unfortunately the metabolism of Imipramine is such that there is a non linear relationship between Imipramine dosage and serum levels. Large variations in the drug levels have been reported [11].Hence this may be an explanation for the large variation in the response rate.

In group II 30% of the cases responded to the Oxybutynin drug treatment. Oxybutinin has antimuscarinic action by high affinity for muscarinic (M1/M3) receptors on the bladder. So it increases FBC and decreases uninhibited bladder contraction or detrusor instability in urinary frequency and incontinence. In group II, 9 cases were continent after the drug administration period and 6 cases were continent after the follow up period. In 1977 Buttarazzi found response rate of 41% in 39 enuretic patients treated with Oxybutinin [12].

In group III, 70% of the cases responded to the Desmopressin (DDAVP) drug. There were 21 continent cases at beginning of follow up period and 14 continent cases at end of follow up period in this group. Desmopressin has favourable response in 10% to 60-70% of cases. Desmopressin (DDAVP) is the synthetic analogue of hormone vasopressin. By selective agonist action on V2 receptors on collecting ducts in kidney it increases cAMP production. Hence it increases water permeability and absorption and thus decreases urine output to less than FBC. Aladjem et al (1982) observed, decrease in number of wet nights from 18.76.5 to 6.59.2 in 15 children treated with DDAVP [13]. Dimson (1986) however reported that only 41% of patients treated with DDAVP had a favourable response with reduction of wet nights from 10.6 to 8.1 wet nights every 2 weeks [14]. Overall response rate of 85% with DDAVP has been reported by Riccabona et al (1998) [15]. In 1998 Cendron and Klauber reported a response rate of 77% with DDAVP (57% patients being completely dry and 21% patients being dry at least 80% of nights)[11].One systematic review (2005) found complete response in 60% of patients treated with DDAVP compared to 13.3% response in placebo group (p=0.02)[12]. In study by Monda and Husmann (1987-94) 68% response rate was found in patients treated with DDAVP [9].

In group I, 76.9% of the responders relapsed in the follow up period. Of 9 responders in group II; 3 (33.3%) relapsed. In group III 33.3% of responders relapsed with increase in wet nights/ month from 1.11.21 (before start of follow up) to 2.2±1.9 (at end of follow up.)

Shaffer et al (1968) had reported a relapse rate of 90% in 62 enuretic children responding to Imipramine[7]. A relapse rate of 84% was reported by Monda and Husmamn on removal of drug therapy in Imipramine responders, after one year of follow up [9]. In follow up of DDAVP treatment responders Uygur et al (1997) found a relapse rate of 36%[16]. However a recent systemic review (2005) has found a relapse rate of only 6.25% among DDAVP responders [12]. Monda and Husnann reported a relapse rate of 90% in DDAVP responders, 6 months after weaning the patient from the medication [9].

Our study showed that 20% of the cases in group I had notable side effects. Group I cases reported side effects of nausea, anxiety and dizziness. The study of Gepertz and Neveus (2004) reviewed records of 49 enuretic children who had been treated with Imipramine. They found that the adverse effects of Imipramine, mostly nausea were experienced by 10 of the 49 (20.4%) children [17]. In group II, 16.7% of the cases reported side effects. Cases in group II complained of dry mouth and constipation. Lovering et al (1998) while studying efficacy of Oxybutinin in 30 enuretic children observed mild side effect (stomach discomfort, fatigue, dizziness, headache, dry mouth) in 5 of the 30 (16.7%) children who completed the study [18]. Of group III cases, 16.7% reported side effects. They mainly complained of nasal irritation with 1 case complaining of pain in legs. Similar incidence of side effects has been reported in the study of 22 patients with NE treated with Desmopressin. In the study 13.6% cases experienced headache and an equal number of cases complained of stomach pain [19]. None of the cases in any of the groups had side effect significant enough to cause withdrawal of the drug treatment. All the three drugs had good compliance rate with all the cases fully compliant in group II, 96.7% cases compliant in group I and 93.3% cases compliant in group III.

In our study, in all the responders who did or did not relapse, the number of wet nights at the end of study was definitely lower than the pre treatment level. It was 3.8±1.71 wet nights/ month for group I cases, 2.67±1.67 wet nights/ month for group II cases and 2.2±1.9 wet nights/ month for group III cases. However in absolute number, the cases that actually fitted in the continent definition adopted by our study were few, and hence qualified for the relapse group. In group I and group II the number of continent cases at the end of study period was 10% and 20% of the total initial cases in each group, in contrast to 46.7% of the total initial cases in group III. This is because Desmopressin had a large number of responders at the end of drug administration period combined with a low relapse rate, hence a better outcome.

CONCLUSION

It is concluded that all the three drugs cause significant reduction in wet nights. However Desmopressin had the highest response rate and the lowest relapse rate. Imipramine had a better response rate than Oxybutinin but it also had the highest relapse rate among the three drugs. All the 3 drugs had minimal side effect, hence the compliance was very good in all the 3 groups.

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