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Review Article

Treatment and Management of Nocturnal Enuresis: A Review

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ABSTRACT

Nocturnal Enuresis (NE) is the involuntary passing of urine whileasleep after the age at which bladder control would normally be prevised. NE has hassled humans for hundreds of years. It has been recognized since the time of Papyrus Ebers, 1550 B.C. Various potions were prepared by using different plants, animals or organs in some of the early treatment modalities. A number of medications have been used to treat nocturnal enuresis where, Imipramine and Desmopressin acetate were found to be efficacious. Besides, some credit has also been given to Oxybutynin. Because of the high relapse rates recited after short-term therapy with pharmacotherapeutic agents, pharmacological treatment for NE is best considered as management therapy rather than a cure. In this review article, we have mainly focused on the treatment and management of nocturnal enuresis by reviewing various treatment modalities along with behavioural modifications, bladder retention training, hypnotherapy, psychotherapy and combination therapy.

Keywords: Bladder retention training, Desmopressin, Enuresis, Hypnotherapy, Imipramine, Oxybutynin, Psychotherapy.

INTRODUCTION

Nocturnal Enuresis (NE) is the involuntary passing of urine during sleep after the age at which bladder control would normally be prevised. It is possibly distressing and disabling situation accounting for the most common pediatric health issues that can have a deep impact on a child or young person's behavior, emotional and social well-being. A child can able to voluntarily void or inhibit voiding during the 2nd and 3rd years of life. Approximately 20% of children have a bedwetting episode at least monthly at 5 years of age[1]. This incidence decreases by 6 years of age to approximately 10%, of which 15% of them consequently attain night time control each year and at least by age 15, only 1% to 2% of adolescents still be enuretic. A male to female ratio was observed to be 3:2. Predominantly, male accounts for a 60% of bed-wetters and more than 90% of night time bed-wetters[2].

History of Nocturnal Enuresis

NE has hassled humans for hundreds of years. It has been recognized since the time of Papyrus Ebers, 1550 B.C. A number of early treatment modalities enfold mistreatment of varied parts from plants or animals or organs. For instance, some counteractions so called 'treatments' enclosed reposing a quill from a hen in apathetic water and making the kid drink it or reposing testicles from a hare into a glass of wine and making the kid to drink it. Some people tried withering the quill of cock and spreading it on the kid's bed who is suffering with enuresis, and another therapy inducing sores/burns on the sacrum of the kid[3]. In 1927, Friedellelucidated with an urge to utilize psychic therapy by constricting fluids and injecting sterile water will yield an affirmative outcome. Regrettably, children are still being taunted/ spanked by their parents for bedwetting. In 1981, a study concluded that 61% of American parents perceived bedwetting as a suggestive problem and one-third of them acted to it by punishing the child.

Pharmacological Treatment

A number of medications have been used to treat nocturnal enuresis where, Imipramine and Desmopressin acetate were found to be efficacious, besides, some credit has also been given to Oxybutynin. Because of the high relapse rates recited after short-term therapy with pharmacotherapeutic agents, pharmacological treatment for NE is best considered as management therapy rather than a cure. Consequently, majority of the patients need long-term therapy either continuously or as on needed basis[1]. An immediate response with a single dose is seen in children who use these medications. As a result, some options to retain the use of such regime for exceptional conditions like overnight parties, or any plans of outdoor living.

Imipramine is a tricyclic antidepressant that is hypothesized to affect NE through three mechanisms of action: (i) alteration in mechanisms of arousal and sleep, (ii) antidepressant action, and (iii) anticholinergic and antispasmodic effects[4]. It may also show its action by increasing ADH secretion from the posterior pituitary[5]. It is taken 1-2 hours before bed time and the duration of action is 8-12 hours. Initial doses are generally 25 mg per day with a maximum dose of 50 mg per day for children of age 8-12 years and children greater than 12 years of age can usually tolerate 75 mg per day if required[2].

Imipramine is usually prescribed for 3-6 months with a gradual termination thereafter. After the cessation of therapy, if the enuretics experience the relapse then they have to use the medication for several months. Initial success rates are as high as 50%. Despite, some studies

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record a combined long-term cure rate of only 25% once the medication is stopped[6]. Some of the uncommon side-effects include dry mouth, mild GI disturbances, nervousness, insomnia, and personality changes[7]. The main complication with Imipramine is the liability of an overdose. Overdosing may cause hypotension, and myocardial effects namely arrhythmias and conduction blockade[8]. Toxic reactions due to drug overdose and deaths have been reported with Imipramine[9, 10]. In spite of distinguishable response from Imipramine, it should be used with caution and the family/parents should be counseled regarding the sustained therapy and the precautions to be taken during administration.

Desmopressin acetate is a synthetic congener of vasopressin that effects by decreasing urine production by means of which water retention and concentration of urine in distal tubules is increased[2]. Desmopressin acetate was approved by Food and Drug Administration (FDA) in1990 and thereby gained extensive use in the United States[1]. It is used intravenously in the treatment of central diabetes insipidus, von Willebrand's disease, and hemophilia A. In 1970s, it was pioneered in the treatment of NE in Europe[11, 12]. This drug is markedly effective in patients with NE who do not exhibit a normal diurnal rhythm of ADH secretion with a consequent decrease in production and high urine output at night. It is available as nasal spray which delivers 10 mcg per spray where the initial recommended dose in the treatment of NE is 20 mcg per spray per nostril[13]. Few children respond to a minimum dose of 10 mcg whereas some require a maximum dose up to 40 mcg per two sprays per nostril to achieve a maximum therapeutic effect.

In 1998, FDA has approved the tablet formulation of Desmopressin acetate for the management of primary nocturnal enuresis (PNE) in children of age 6 and above. This oral form is available as 100 and 200 mcg (0.1- 0.2 mg) tablets and the suggested dose ranges from 200-600 mcg (0.2 – 0.6 mg) to attain desired therapeutic outcome. Various studies demonstrated favorable results with this oral form of Desmopressin acetate in comparison with the intranasal form[14, 15]. Enuretics may choose the oral form because they may either experience nasal congestion with the use of nasal spray which may consecutively obstruct the absorption of medication. Some children may find complicated to administer nasal spray by themselves. Another aspect is that the oral form is much more sensible and often does not need an explanation if the child is taking the medication in front of others.

Instantaneous effects are usually observed with this medication. Nevertheless, the literature presents that the stated range of response to Desmopressin acetate alters from 10% to 91%[16]. In 1996, Husmann elucidated that 68% had a full response when Desmopressin acetate was used in the treatment of monosymptomatic NE, whereas in patients with both diurnal and nocturnal enuresis, only 19% were found to be effective. The response to Desmopressin acetate also emerges to be dose related[17, 18]. The duration of therapy differs with each patient and is dependent on the clinician where some recommend 2 weeks of therapy and taper the dose, while, others treat at an effective dose for months with periodic trials to evaluate for dryness. High relapse rates are observed after discontinuation of short-term therapy restating that this type of therapy is considered useful as a management therapy rather than a long-term cure. Thereby, Desmopressin acetate is usually recommended for substitution therapy[19]. The use of Desmopressin acetate is usually reserved for situations like overnight stays away from home in children who attain instantaneous outcome.

If used precisely, Desmopressin acetate is safe and sound. Some disclosed side-effects of the nasal spray form are nasal congestion, mild headache, rhinitis, and epistaxis whereas the tablet form has disclosed the side-effects of mild headache[20]. Very rare cases of hyponatremia secondary to water intoxication can also be seen[21, 22]. Most of these cases occurred because of excessive fluid intake in combination with taking the medication. It is of extreme concern to ensure that both the patient and family should understand the significance of fluid restriction in combination with taking the medication. By illustrating the action of Desmopressin which is characterized by the temporary reabsorption of water from the kidney, majority will understand its significance. In order to seek prior medical attention, parents should be alert to some preceding signs of water intoxication which includes blurred vision, altered level of consciousness, confusion, disorientation and frontal headache. Often, advancement of symptoms is prognostic of a fall in the serum sodium level and is usually succeeded by a seizure[23]. The clinician must evaluate the existence of other factors like cystic fibrosis, renal disorders and endocrine disorders that might produce electrolyte imbalances prior to prescribing Desmopressin acetate. Both psychogenic polydipsia and habit polydipsia should be taken into account because of the risk of water intoxication and hyponatremia[2, 24]. Patients and their families should be cautioned not to use Desmopressin acetate in conditions like fever, viral ill health, vomiting, and diarrhea where fluid and electrolyte balance are affected. Increased intake of fluids is recommended for treating such conditions which would consider the ingestion of Desmopressin acetate spurious.

Anticholinergic medications, distinctively Oxybutynin, have the characteristics of a muscle relaxant, where it reduces the unrestrained bladder contractions and the local anesthetic effects on the bladder as well. Thereby, this medication would hypothetically assist the bed-wetter by enhancing the bladder capacity[25]. This mode of action may be helpful to those children who are also presented with daytime urgency and/or incontinency or frequency. About 90% of success rates have been reported in enuretic children with significant daytime incontinence and/or bladder inconsistency[26]. Nevertheless, anticholinergics are unusually helpful for children with confined nocturnal enuresis[27].

Behavioral Modifications

Studies during 1970s and 1980s reported that <5% of physicians incorporated behavioral treatment instead of pharmacotherapy. "Motivational therapy" is a kind of behavioral reconciliation assisting positive support using applause and benefits. To keep record of dry nights, a behavioral chart namely, "star chart" is used where the

parents and the physician contribute positive support and or rewards. By considering alone, the motivational therapy accounts for an estimated cure rate of 25%. However, noticeable progress in more than 70% of patients has been recorded[2]. The fundamentals of motivational therapy can be incorporated into other therapeutic regimens like pharmacologic therapy and conditioning.

"Conditioning therapy" incorporates an enuretic alarm system which uses a signal alarm that is triggered by contact of urine. Its presumption is to make the child awake to the sensation of a full bladder. This is the most commonly suggested form of therapeutic regimen as depicted in medical literatures. A success rate of 65% to 75% and proportionately low rates of relapse were observed[28]. The bell and pad alarm system is an earlier system where the child sleeps on a sensory pad and alarm is set off only after the child's undergarments are soaked out. But these newer systems are adhered to the clothing at the place of the perineum which is provoked at the commencement of urination instead after the child has partially or completely emptied the bladder. By recurrent acquaintance of awakening to the alarm, the persuasion feature of awakening simultaneously with suppression of voiding is progressively evinced.

Various alarms are accessible that are compact and easily susceptible for the child to perform. Most of these systems are incorporated with an audio alarm that transmits a sound of 80db. A tangible alarm that is attired near the bladder vibrates with the sensation of wetness is accessible. This alarm has the benefit of signaling the child alone and not awakening the rest of the household as is frequently the case with audio alarms.High success rate with low relapse rate are the benefits of this system. Those children in whom relapses occur often respond to a short second course of therapy by using the alarm. As many parents prefer medication therapy to someextent, this alarm form of therapy is considered to be beneficial. The drawbacks of this alarm system are that they are time exquisite and need a higher degree motivation and assistance from the child and also the family for a minimum of 3 weeks and a maximum of 4-6 months. But a repetitive curbing may be seen in the family if the child does not awake to the alarm[29,30].

Bladder-Retention Training

This is based on the postulation that the child has a declined bladder functioning capacity. In order to endow a baseline, assurance of normal bladder capacity for each age group is recommended using the following formula: Bladder capacity (in ounces) = Age (in years) + 2[31]. Bladder-retention training includes conscious endeavors at bladder stretching by prolonging the intervals between voiding voluntarily. This training also includes cultivating a daily log of volumes voided, forcing fluids throughout the whole day and stream hindrance. The basic postulation of this therapy is that an increase in the bladder capacity will make feel better or drive out the enuresis. The aspect of fluid restriction before bed time is usually conversed with parents. Out of anguish most patients restrict fluids before bed time. Usually, it works but majority find that it is a provenience of curbing and that may lead to conflict between the child and parent. Statistical evidence depicted that fluid restriction is not effective[32]. A cure rate of only 35% is esteemed for bladder-retention training[33]. This is probably due to the stringent nature of the method and the aspect of bladder instability and urinary frequency seen in some of those children.

Hypnotherapy

Hypnotherapy includes the explanation regarding the bladder-brain linking and illustrating the self-hypnosis and visual imaging to the child to act in response to full bladder during asleep. A 76% of dryness rate after endowing both types of treatment was reported in one controlled study comparing hypnotherapy with Imipramine. Succeeding a period of 9 months, 68% of the hypnotherapy group stays dry in comparison to only 24% in the imipramine group[4].

Psychotherapy

Without a plausible evidence of its efficacy, psychotherapy has been used as a treatment for enuresis. Werry described that most of the primary enuretics do not experience or complain of underlying psychoneurosis. As sustained psychoanalysis is usually an ineffective and inessential approach for children with PNE, it should be precised to children with distinct psychopathology[34].

Combination Therapy

Combination therapy is usually recommended when a definite therapy is not efficacious. A sort of such combined therapeutic modalities constitute Desmopressin, behavioral modification and the enuresis alarm[35]. The incentive for this combination is patient/parent contentment due to the certitude that Desmopressin may have an instantaneous outcome and the enuresis alarm may take around 3 weeks to observe a subsidence in wet nights[36]. In primitive treatment period, parents usually discontinue using the enuretic alarm as a result of uninterrupted enuresis[37]. It is affirmed to enhance compliance by endowing Desmopressin during the commencement of alarm therapy. One report depicts thatsucceeding 3 weeks of enuresis alarm/Desmopressin combination, a gradual termination of the Desmopresin and ensuing therapy of the alarm and behavioral modification can enhance a cure of the enuresis. Combination of Imipramine and Desmopressin acetate has been efficacious in some patients with refractory primary nocturnal enuresis. The synergistic action between the two medications causes decreased urine production, increased bladder capacity and easier awakening which has yielded an assured positive outcome[38].

CONCLUSION

Deliberations should be made for the proper outcome of NE since there might be comorbid symptoms that require diligence either prior or during the treatment. In addition to this, patient/family education with a cooperative commencement will produce affirmative outcomes in treating NE. Majority of the general practitioners are uninitiated and inexperienced about the issue. This may be as a result of either or both patient's and family's unwillingness to talk about it or obtaining history may be time consuming or examination may be bewildering.

However when affirmed results were gained with the help of various methods of treatment, it promises to be a dream come true for the patient and the family and as well as for the practitioner's achievement of expected outcome.

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