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Original Article

Evaluation of Intralesional Injection of Combined Furosemide and Digoxin Formula in the Treatment of Warts

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Abstract

Background: Warts are benign growths that appear on the skin or mucous membranes as a result of an infection with the human papillomavirus [HPV]. Few prior investigations examined the efficacy of a topical combination of digoxin and furosemide for the treatment of warts. The study to assess and confirm the effectiveness of intralesional ionic antiviral injections that mix digoxin and furosemide for the treatment of multiple resistant plantar warts

Patients and Methods: An interventional trial with two arms was conducted. Thirty plantar warts patients in all were chosen from the Al-Azhar University Hospital's outpatient clinics for dermatology, andrology, and venereology.

Results: The mean number of sessions for the studied cases was 5.17 [±0.91 SD] with a range of 4-6. Of the studied cases, 23 [76.7%] had pain, 7 [23.3%] had hemorrhagic bulla and pain with a pain score of 6 [±2.36 SD], and 23 [100%] of completely treated cases had no recurrence. Of the studied cases, 2 [6.7%] had no response, 5 [16.7%] had partial clearance, and 23 [76.7%] had complete clearance. Following treatment, the largest wart's mean size was 0.14 [±0.34 SD] with a range of 0–1.5 and the mean number of warts was 0.43 [±0.86 SD] with a range of 0–3. We discovered a statistically significant relationship between the kind of clearance and the number of sessions, age, and duration of the condition.

Conclusion: Our findings suggest that intralesional injection of digoxin and furosemide together is a successful treatment for numerous plantar warts.

Keywords: Warts; Intralesional Injections; Furosemide; Digoxin.

INTRODUCTION

Verrucae, also known as cutaneous warts, are a common benign skin ailment that affects 3–13% of people in the Western world on average. At some time in their lives, the majority of people develop cutaneous warts [1]. Human papilloma virus [HPV] is the cause of cutaneous warts. HPVs 1, 2, 27, and 57 are linked to the vast majority [> 80%] of verrucae in the general population. It is commonly recognized that papillomaviruses require the environment to proliferate. More precisely, research has demonstrated that potassium ion influx is necessary for the replication of HPV [2].

Outside of the anogenital region, mouth or throat tissues can sometimes get infected with external genital warts after oral sexual contact with an infected partner [3]. Condyloma acuminata can be with different shapes and their appearance is very diverse. Although lesions are rarely thought to be uncomfortable, they are frequently linked to excruciating pain, burning, and pruritis. Furthermore, larger lesions could bleed and become irritated when they come into touch with clothing or during sex [4]. Even while cutaneous warts are benign and typically go away on their own, they can be uncomfortable both physically and psychologically. A wide range of wart-removing products are used by many patients [5]. The two types of treatments are topical agent application or ablative [vaporization, resection, coagulation, or excision]. While physically ablative therapies are more effective in eliminating warts, topical medications are frequently the first choice of patients, particularly for minor lesions [6].

Potassium Ion influx is necessary for the replication of viruses like HPV. By interacting with cell membrane ion co-transporters, digoxin and furosemide both block the potassium Ion inflow [6]. Digoxin and furosemide together had the strongest inhibitory effect on DNA replication, according to **Hartley *et al.*** [7]. It is proposed that local administration of this novel strategy, known as ionic contraviral therapy [ICVT], which combines two well-known, proven medications, will yield the best results. **Van der Kolk *et al.*'s** [8] assessment of the systemic exposure, safety, and tolerability of intracutaneous cetaceous wax ICVT using a furosemide and digoxin combination followed repeated topical administration in individuals with common warts. When comparing treated and untreated warts at day 4, they revealed a rapid and statistically significant decrease in the warts' size. Thus, it is possible that these two substances, when used topically, could be helpful in the management of warts caused by HPV. Ionic Contra-Viral Therapy [ICVT] is the name of this novel strategy.

In order to treat numerous resistant plantar warts, the current study set out to assess and confirm the safety, tolerability, and efficacy of intralesional ionic antiviral injections that combined digoxin and furosemide.

PATIENTS AND METHODS

The current investigation was Thirty plantar warts patients in all were selected from the Al-Azhar University Hospital's Outpatient Clinic of Dermatology, Andrology, and Venereology Department for a double-arm intervention. Written consent was obtained from all participants. The clinical research study was carried out in compliance with the most recent IRB-approved clinical protocol, the applicable policies, rules, and regulations of Al-Azhar University, and the ICH GCP Guidelines.

Our study comprised patients with three or more plantar warts and two sexes between the ages of 20 and 50. Female patients who were pregnant or nursing, patients who had undergone topical medication or ablative [vaporization, resection, coagulation, or excision] treatment on the lesions within 30 days of the study's start, systemic use of corticosteroids, zinc, vitamin D, and other immunosuppressive or immunomodulatory drugs within 30 days after study enrollment or throughout the trial, a documented sensitivity to any of the components in the experimental product, Our study did not include any clinically significant aberrant laboratory values, ECG, vital signs, or physical findings at screening.

Every patient in the current study underwent a thorough history taking, a full general checkup, a dermatological examination, an ECG to identify any cardiac issues, and ongoing monitoring of their heart health. Test a urine sample for hazardous or abnormal digoxin and furosemide levels.

We prepared 20 ml of combined digoxin and furosemide, therefore [0.01 25×20] ÷1 00=0.025/1 ml indicates that 0.025 ml of both furosemide and digoxin are present in every 1 ml of prepared solution. The dose per milliliter of solution is 0.025. Injectable dose: 0.025 ÷3 = 0.0083/ml Digoxin [0.1 6 mg] with furosemide [0.1 6 mg] were calculated as follows: For 20 ml of injectable solutions, there are 0.16 mg of furosemide and 0.0083 × 20= 0.16 mg of digoxin. Thus, the maximum number of warts per session for five sessions was five at a dosage of 0.0008 mg/ml per wart

A clinical ruler was used to measure the height and diameter of the wart, and the change in wart volume [mm^3] was used to determine the clinical ruler [8]. Signs of toxicity include fast heartbeat, irregular pulse, nausea, vomiting, diarrhea, and changes in vision both before and after the research is over. Dermoscopic examination and digital pictures are also indicators of toxicity. Following the final session, patients were monitored for six months. Records were kept on the outcomes, complications, and patient satisfaction.

Statistical analysis: The computer was fed data, and IBM SPSS software package version 20.0 was used for analysis. [IBM Corp., Armonk, NY] Numbers and percentages were used to describe the qualitative data. The distribution's normality was confirmed using the Kolmogorov-Smirnov test. For regularly distributed quantitative variables, one-way ANOVA was utilized to compare data from more than two research cohorts. When comparing two periods of abnormally distributed quantitative variables, the Wilcoxon test was employed.

RESULTS

There were 15 [50%] female and 15 [50%] male cases in the study, with a mean age of 31.87 [±10.12 SD] and a range of 18–50 years. The mean disease duration was 11.47 [±16.31 SD] with a range of 1–72 months [Table 1]. Of the cases under study, 10 [33.3%] had undergone prior therapy, of whom 5 [16.7%] underwent surgery, 7 [23.3%] underwent cryotherapy, and 1 [3.3%] underwent electrotherapy [Table 2]. The mean number of sessions for the studied cases was 4.17 [±0.41 SD] with a range of 4-6. Of the studied cases, 23 [76.7%] had pain, 7 [23.3%] had hemorrhagic bulla and pain with a pain score of 6 [±2.36 SD], and 23 [100%] of completely treated cases had no recurrence. Of the studied cases, 2 [6.7%] had no response, 5 [16.7%] had partial clearance, and 23 [76.7%] had complete clearance [Table 3].

Between the wart data collected before and after treatment, there was a substantial statistical change [Table 4]. A statistically significant relationship was found between the kind of clearance and the duration, number of sessions, and age of the disease [Table 5].

Table [1]: Demographic data of studied cases

		Cases [no=30]	
Age	Range	18 – 50	
	Mean ± SD	31.87 ± 10.12	
Gender	Female	15	50.0
	Male	15	50.0
Disease duration	Range.	1 – 72	
	Mean ± SD.	11.47 ± 16.31	

Table [2]: Previous therapy of studied cases

		Cases [no=30]	
		No.	%
Previous therapy	No	20	66.7
	Yes	10	33.3
Type of therapy	Surgery	5	16.7
	Cryotherapy	7	23.3
	Electrotherapy	1	3.3

Table [3]: The outcome of the studied cases

		Cases [no=30]	
		No.	%
Type of clearance	No response	2	6.7
	Partial	5	16.7
	Complete	23	76.7
Number of sessions	Range.	4 – 5	
	Mean ± SD.	4.17 ± 0.41	
Side effects of treatment	Hemorrhagic bulla & pain	7	23.3
	Pain	23	76.7
Pain score	Range.	1 – 10	
	Mean ± SD.	6 ± 2.36	
Recurrence	No	23	100.0

Table [4]: Wart data before and after treatment

		Cases [no=30]		Test	p
		Before	After		
Number	Range.	1 – 5	0 – 3	4.049	<0.001*
	Mean ± SD.	2.9 ± 1.4	0.43±0.86		
Size of largest one	Range.	0.2 – 2	0 – 1.5	4.797	<0.001*
	Mean ±SD.	1.04±0.6	0.14±0.34		

Z: Wilcoxon test

Table [5]: Relation between Type of clearance and different parameters

		Cases [no=30]			Test	p
		No response	Partial	Complete		
Age	Range.	35 – 49	30 – 50	18 – 50	5.08	0.013*
	Mean±SD.	42 ± 9.9	41 ± 10.25	29 ± 8.63		
gender [n,%]	Female	1[50]	2[40]	12[52.2]	0.24	0.885
	Male	1[50]	3[60]	11[47.8]		
Disease duration	Range.	12 – 48	2 – 72	1 – 24	7.17	0.003*
	Mean±SD.	30 ± 25.46	28 ± 30.63	6.26 ± 5.37		
No of session	Range.	5 – 5	5 – 5	4 – 5	4.81	0.015*
	Mean±SD.	5± 0	5± 0	3.91 ± 0.5		

DISCUSSION

Warts are microscopic, benign growths on the skin or mucous membranes that result from HPV infection [9]. Warts can spread directly between individuals or indirectly through fomites. The major targets of HPV infection are basal keratinocytes, which may be reached by HPV via maceration of the epithelia [10]. As of yet, there is no cure that works 100% of the time. Costs and side effects, such as discomfort from the treatment, may influence the therapy that is selected. Even with a single medication, reported efficacies can differ greatly and rely on a number of factors, including the technician's ability, immunocompetence, wart location, application technique, and compliance. It's also vital to be informed of alternate therapies for resistant warts because occasionally viruses may linger in the skin after treatment and cause the development of new warts later [11].

Potassium influx is necessary for DNA viruses like HPV to replicate. Digoxin, a cardiac glycoside, and furosemide, a loop diuretic, both work by interacting with co-transporters of ions in cell membranes [Sodium ion/potassium ion-ATPase and sodium ion-potassium ion-chloride ion − co-transporter-1]. It is therefore believed that these two substances could be useful in the management of warts caused by HPV. We refer to this novel strategy as ionic contra-viral treatment [12]**.** The topical combination of furosemide and digoxin for the treatment of warts has been the subject of very few previous trials. Considering the paucity of previous studies evaluating the efficacy of intralesional injection of digoxin and furosemide in combination for the treatment of warts [13].

In order to treat multiple resistant plantar warts, we therefore carried out our study with the goal of assessing and confirming the effectiveness of intralesional ionic antiviral injection combination with furosemide and digoxin. An interventional trial with two arms was conducted. Thirty plantar warts patients in total were chosen from the Al-Azhar University Hospital's outpatient clinics for dermatology, andrology, and venereology. Based on our data, the analyzed cases had a mean age of 31.87 [±10.12 SD] with a range of 18–50 years, 15 females and 15 males, and a mean disease duration of 11.47 [±16.31 SD] with a range of 1-72 months. Eighty individuals with cutaneous warts diagnosed clinically and dermoscopically were included in **Lofty *et al.*'s** [14] study; the age range of the patients was 18 to 50 years, with 42 females and 38 men [52.5% and 47.5%, respectively].

Ten females [50%] and ten males [50%] made up the ionic contra-viral cohort in the study by **Fathy *et al.*** [13]**;** their ages ranged from 18 to 43 years [Mean ± SD; 28.6 ± 8.6 y], and their length of illness varied from 2 to 28 weeks [Mean ± SD; 11 ± 8.5 w]

Ten of the cases under investigation in this study had previously had therapy; of these, five underwent surgery, seven received cryotherapies, and one received electrotherapy. Additionally, the largest wart's mean size prior to therapy was 1.04 [±0.6 SD] with a range of [0.2-2] and the mean number of warts prior to treatment was 2.9 [±2.4 SD] with a range of 1–9. Before treatment, wart sizes in the ionic contraviral cohort varied from 2 to 6 mm [mean ± SD; 3.8 ± 0.9 mm]. In the ionic contraviral cohort, the mean ± SD [4.0 ± 0.9] number of warts per patient ranged from 3 to 5. There were a total of 80 warts in the ionic contraviral cohort prior to treatment [13]**.**

Among the cases that were studied, we discovered that 2 had no response, 5 had partial clearance, and 23 had complete clearance. The mean number of sessions for the cases that were studied was 5.17 [±0.91 SD] with a range of [4-6]. Of the cases that were studied, 23 had pain, and 7 had hemorrhagic bulla and pain with a pain score of 6 [±2.36 SD]. Of the cases that were studied, 23 had no recurrence. Based on the response grade, 37 patients had a complete clearance of warts, 2 patients had a partial response, and 1 patient had no response to therapy [14].

There were 40 lesions that responded very well, 21 lesions that responded very well, 10 lesions that responded well, and 9 lesions that responded poorly. All patients reported discomfort during injection, according to the assessment of side effects and consequences; the pain became more noticeable with the active treatment. Erythema, edema, ulcers, and suppuration were not observed as adverse effects [13].

According to our data, the largest wart's mean size after treatment was 0.14 [±0.34 SD] with a range of 0–1.5, and the mean number of warts after treatment was 0.43 [±0.86 SD] with a range of 0–3. Intralesional combination digoxin and furosemide injections were performed by Fathy et al. [13] once a week, up to a maximum of five injection sessions. They discovered that there were 80 warts prior to treatment, but there were only 40 warts after treatment [a 50% decrease in wart count]. The number of sessions required for full removal varied from 3 to 5 [mean ± SD; 3.9 ± 0.9]. When comparing treated and untreated warts, **Van Der Kolk *et al.*** [8] found that a rapid and statistically significant reduction in the warts' diameter, height, and volume was already observed at day 14 [diameter end-of-study, -0.29 mm, 95% CI −0.43/−0.15, P-value = 0.0003; height end-of-study, −0.52 mm, 95% CI −0.75/−0.30, P-value = <0.05; volume end-of-study, −68.3 mm3, 95% CI −105.4/−31.2, P-value = <0.05]. This open-label study, however, cannot completely rule out observer bias. Additionally, for seven days straight, a fixed dose of 980 mg topical gel comprising 0.125% [w/w] digoxin and 0.125% [w/w] furosemide was administered.

We discovered a statistically significant relationship between the kind of clearance and the number of sessions, age, and duration of the condition. Comparably, **Fathy *et al.*** [13] showed that patients who responded well or poorly could respond better if they received more treatment sessions, more warts were treated during each session, fewer sessions were spaced apart, or more concentrated active treatment.

Furthermore, compared to warts that had been present for more than six months, those that had been present for six months or less had a higher chance of clearing within three months, according to Ahmed et al. Additionally, Berth-Jones and Hutchinson found that lesion size and disease duration were important determinants of response [15, 16]. However, they could not discover any statistically significant relationship between the length of the disease, age, or sex and the response to treatment [reduction in number] [13].

Previous research did not account for confounding variables, therefore variations in the statistical techniques employed may contribute to this discrepancy. To highlight our findings, more research over a wider geographic area, with a larger sample size and a longer follow-up period, is required. Additionally, a significant number of additional trials from other centres will be required to assess and confirm the effectiveness of intralesional ionic antiviral injections combined with digoxin and furosemide in the treatment of numerous resistant plantar warts [16].

Conclusion: When treating numerous plantar warts, intralesional injection with a combination of digoxin and furosemide is an effective alternative.

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