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A Novel and Cheap Vasoactive Drug Combination for Pharmacological Erection

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Abstract

Introduction: Intracavernosal injection for pharmocological erection is an important tool for diagnosis and treatment of erectile dysfunction. Commonly the three drugs Papaverine, Phentolamine and Prostaglandin E1 have been used either alone or as combinations. *Aim*: To determine the efficacy and safety of a bimix combination of Papaverine and Chlorpromazine administered intracavernosally in patients with erectile dysfunction(ED) of various origins as compared to Papaverine alone. *Methods*: This was a randomized prospective comparative dose titration study as a part of diagnostic armamentarium in the evaluation of erectile dysfunction. Two hundred forty patients diagnosed with Erectile dysfunction were enrolled Injection was subsequently titrated to the dose producing an effective response i.e. an erection sufficient for vaginal penetration lasting for atleast 20 minutes with atleast 48 hrs interval between the successive doses. The response was measured in terms of time for erection(latency period),grade of erection and duration of erection. Any adverse effect or complications were noted. *Results*: Satisfactory erectile response was 85% with Papaverine-CPZ combination in the dose range of 0.1 to 1 ml and and 65% with Papaverine alone in the dose range of 15 to 60 mg respectively. Of 42 men who had failed erection with 60mg of Papaverine, 18 produced erection with Papaverine-CPZ combination. Incidence of prolonged erection were 10% and 12.5% in PPV and Combination groups respectively. Altogether 56 adverse events occurred. 12.5% in PPV alone and 15% in combination group had erection lasting for more than 4 hrs and were aborted by intracavernosal injection of Phenylephrine. 10 in PPV alone and 5 in Combination had penile pain. Eight patients in PPV group had penile haematoma which resolved spontaneously whereas there was no haematoma reported in the combination group. Patients were followed up for a maximum of four years. Seven patients developed fibrotic plaque in the PPV group and there was none in the combination group. *Conclusion*: Papaverine-CPZ combination has proved a cheap and effective alternative to other combinations with better efficacy than Papaverine alone. Side effects like penile pain, hematoma and fibrotic plaque formation was significantly less in the combination group.

Keywords: Erectile Dysfunction; Intracavernosal Vasoactive Agents; Pharmocological Erection.

Introduction

Despite the introduction of 5 phosphodiesterase inhibitors (Sildenafil, Tadalafiletc), intracavernosal-injection therapy remains a popular and very effective mode of therapy for erectile dysfunction (ED). Popularized in the early 1980's, self-administered penile injections had an instant appeal as an alternative to the only available treatment at the time, the penile prosthesis.It has been used successfully for both diagnosis and treatment. It began with the development of Papaverine by Virag [1] and later Phenoxybenzamine by Brindley [2]. The principal drugs used are Papaverine, Phentolamine and Prostaglandin E1 alone or in combination as bimix

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or trimix solutions [3]. Other agents are Phenoxybenzamine, Thymoxamine, VIP (Vaso active intestinal polypeptide) [4], Atropine, Sodium nitroprusside etc.

Phentolamine and Prostaglandin E1 are quite costly and are not readily available in the Indian market. Papaverine alone is not always as effective as PGE1 or bimix or trimix of the above drugs. So a drug which was easily available, cheap and could be combined with Papaverine to give similar results was much sought for. In this study a new bimix combination of Papaverine and Chlorpromazine has been tried . Like Phentolamine, Chlorpromazine is a sympathetic blocker. It is easily available in the market and is quite cheap. It is marketed as 2 ml ampoule with each ml containing 25 mg of Chlorpromazine. The aim of our study was to determine the efficacy and safety of bimix combination of Papaverine and Chlorpromazine administered intracavernosally in patients with erectile dysfunction(ED) of various origins as compared to Papaverine alone.

Methods

This is a randomized prospective comparative dose titration study of a bimix solution of Papaverine-Chlorpromazine with Papaverine alone as a part of diagnostic armamentarium in the evaluation of erectile dysfunction. From January 2009 to December 2013, Two hundred forty patients diagnosed with Erectile dysfunction were enrolled. Each patient received 15mg of Papaverine or 0.1 ml of combination. (Preparation: Mix 19.5 ml (585mg) of Papaverine + 0.5 ml (12.5mg) of Chlorpromazine to prepare 20ml of working solution containing per ml 29.25mg Papaverine and 0.62mg of Chlorpromazine.)

In cases of severe vasculogenic ED, the starting dose was 0.5 ml of combination or 60 mg of Papaverine. Injection was subsequently titrated to the dose producing an effective response i.e. an erection sufficient for vaginal penetration lasting for atleast 20 minutes with atleast 48 hrsinterval between the successive doses. On each dosing day patients were evaluated over a period of 2 hours for response and vital signs (respiratory rate, blood pressure and heart rate). Patients were discharged only after detumescence had occurred. The response was measured in terms of time for erection (latency period), grade of erection and duration of erection. Any adverse effect or complications were noted.

Statistical Analysis

Linear variables were summarized as means & standard deviations (SD) and were compared by using two tailed unpaired 't' test. Nominal/ categorical variables were expressed as proportions and were compared by using Chi-square test. A 2-sided $p<0.05$ was taken as significant.

SPSS 22.0 version software was used for all statistical calculations.

Results

Fifty one percent and forty eight percent patients had ED of Non Psychogenic origin respectively in two groups. Satisfactory erectile response was 85% with Papaverine-CPZ combination in the dose range of 0.1 to 1 ml and and 65% with Papaverine alone in the dose range of 15 to 60 mg respectively. Of 42 men who had failed erection with 60mg of Papaverine, 18 produced erection with Papaverine-CPZ combination.

Incidence of prolonged erection were 10% and 12.5% in PPV and Combination groups respectively.

The mean lowest effective dose for combination was calculated as 0.27ml ±0.15 ml and for Papaverine 32 ± 2.5mg. The mean duration of response was 35 and 40 minutes respectively. Latency period ranged from 2 to 20 minutes with 60% of Papaverine group and 70% of combination group responding within 10 minutes. Altogether 56 adverse events occurred. 12.5% in PPV alone and 15% in combination group had erection lasting for more than 4 hrs and were aborted by intracavernosal injection of Phenylephrine. 10 in PPV alone and 5 in Combination had penile pain. Eight patients in PPV group had penile haematoma which resolved spontaneously whereas there was no haematoma reported in the combination group. Patients were followed up for a maximum of four years . Seven patients developed fibrotic plaque in the PPV group and there was none in the combination group. No other complications were seen.

Table 1: Age

Group	N	Mean	Std. Deviation	'p' Value*
A	120	34.27	9.912	0.834
B	120	34.54	10.37	

*Unpaired't' test

Aetiology	Group A		Group B		Total	
	No.	%	No.	%	No.	%
Non-psychogenic	58	48.33	62	51.67	120	50.00
Psychogenic	62	51.67	58	48.33	120	50.00
Total	120	100.00	120	100.00	240	100.00

Chi-square = 0.150 with 1 degree of freedom; P = 0.699

Erection	Group A		Group B		Total	
	No.	%	No.	%	No.	%
Yes	78	65.00	102	85.00	180	75.00
No	42	35.00	18	15.00	60	25.00
Total	120	100.00	120	100.00	240	100.00

Chi-square = 11.756 with 1 degree of freedom; P = 0.000

Table 2: Doses

Group	N	Mean	Std. Deviation	Median	95% CI	Range
A	78	32.88	13.47	30.00	29.89-35.87	15 to 60
B	102	0.28	0.13	0.01	0.26-0.31	0.1 to 0.6

Table 3: Latency

Group	N	Mean	Std. Deviation	'p' Value*
A	78	10.66	13.33	0.067
B	102	7.882	6.431	

*Unpaired't'test

Duration	Group A		Group B		Total	
	No.	%	No.	%	No.	%
< 1 hr	60	76.92	63	61.76	123	68.33
1-2 hr	3	3.85	20	19.61	23	12.78
2-3 hr	0	0.00	1	0.98	1	0.56
> 4 hr	15	19.23	18	17.65	33	18.33
Total	78	100.00	102	100.00	180	100.00

Chi-square = 10.905 with 3 degrees of freedom; P = 0.016

Prolonged Erection	Group A		Group B		Total	
	No.	%	No.	%	No.	%
Present	13	16.67	16	15.69	29	16.11
Absent	65	83.33	86	84.31	151	83.89
Total	78	100.00	102	100.00	180	100.00

Chi-square = 0.001 with 1 degree of freedom; P = 0.978

Penile Pain	Group A		Group B		Total	
	No.	%	No.	%	No.	%
Present	11	9.17	3	2.50	14	5.83
Absent	109	90.83	117	97.50	226	94.17
Total	120	100.00	120	100.00	240	100.00

Chi-square = 3.717 with 1 degree of freedom; P = 0.054

Haematoma	Group A		Group B		Total	
	No.	%	No.	%	No.	%
Present	6	5.00	1	0.83	7	2.92
Absent	114	95.00	119	99.17	233	97.08
Total	120	100.00	120	100.00	240	100.00

Chi-square = 2.354 with 1 degree of freedom; P = 0.125

Plaque	Group A		Group B		Total	
	No.	%	No.	%	No.	%
Present	7	5.83	0	0.00	7	2.92
Absent	113	94.17	120	100.00	233	97.08
Total	120	100.00	120	100.00	240	100.00

Chi-square = 5.297 with 1 degree of freedom; P = 0.021

Table 4: Doses

Group	Aetiology	N	Mean	Std. Deviation	'p' Value*	Median	95% CI	Range
A	NP	14	49.29	12.38	<0.001	52.50	42.80-55.78	30 to 60
	P	64	29.30	10.83		30.00	26.65-31.95	15 to 60
	Total	78	32.88	13.47		30.00	29.89-35.87	15 to 60
B	NP	44	0.40	0.08431	<0.001	0.40	0.37-0.42	0.2 to 0.6
	P	58	0.20	0.08385		0.20	0.18-0.22	0.1 to 0.5
	Total	102	0.28	0.13		0.30	0.26-0.31	0.1 to 0.6

*Unpaired 't' test

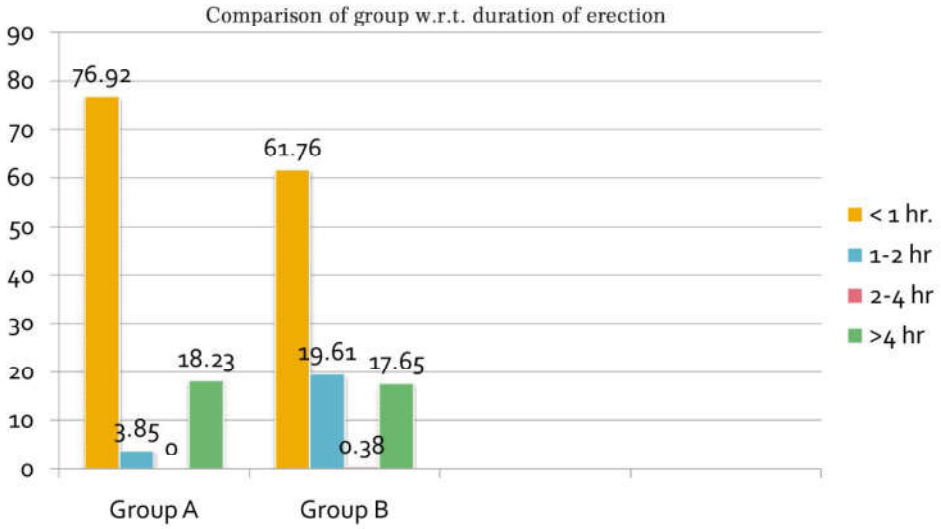

Fig. 1: Comparison of groups with respect to duration of erection

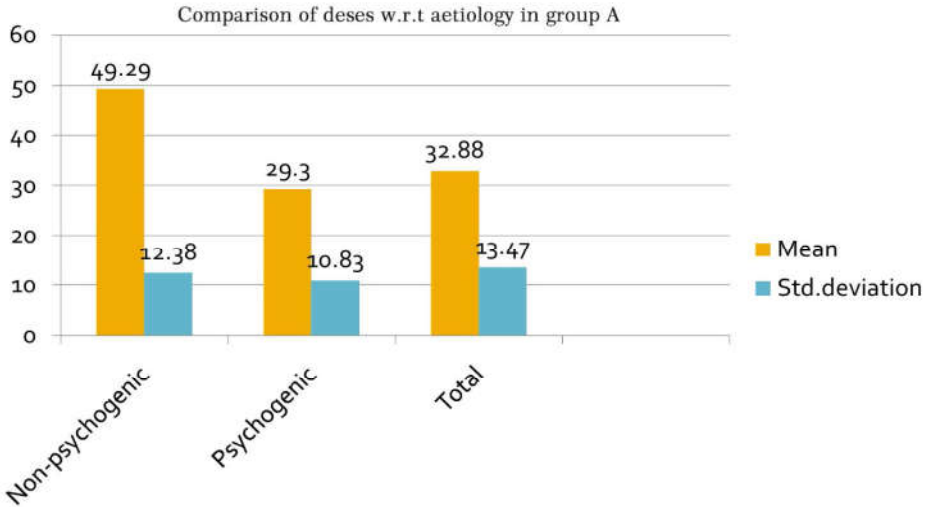

Fig. 2: Comparison of doses with respect to aetiology in two groups

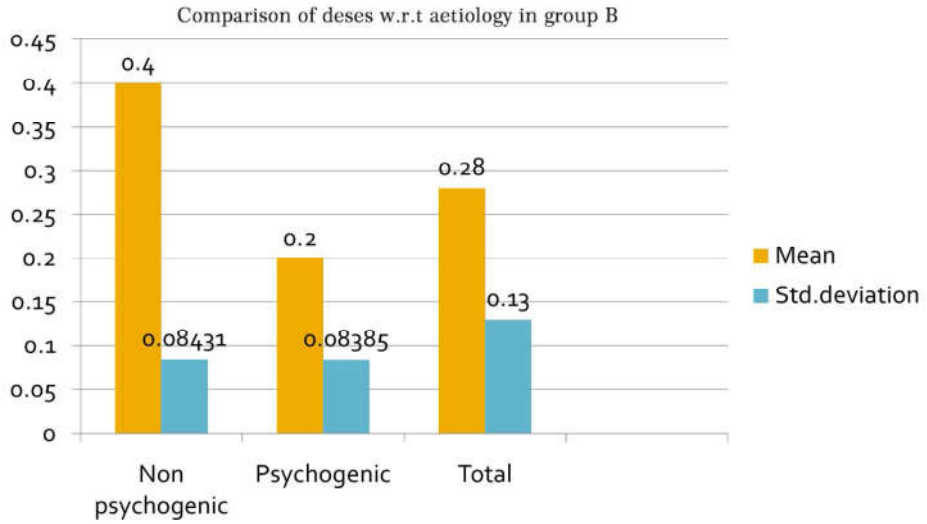

Fig. 3: Comparison of doses with respect to aetiology in two groups

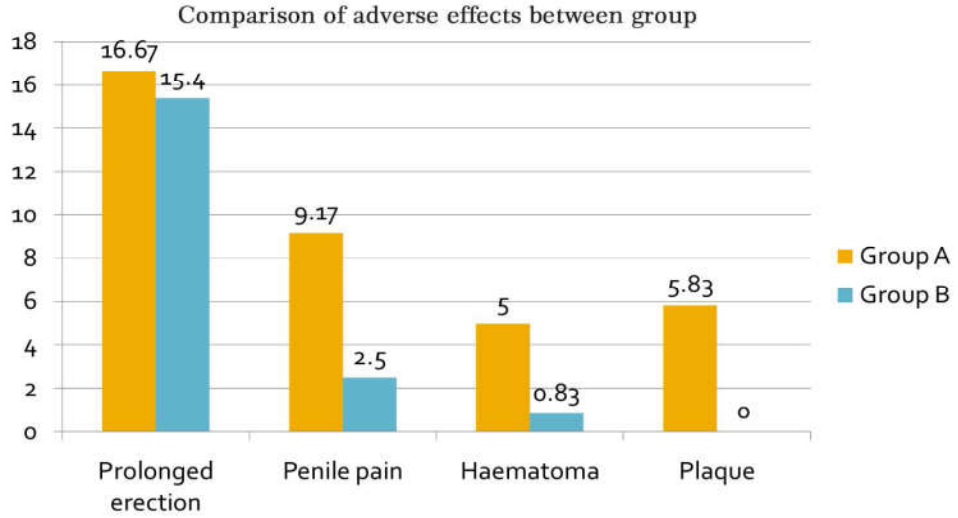

Fig. 4: Comparison of adverse effects between groups

Discussion

The use of intracavernosal injections of vasoactive drugs has proved to be an invaluable tool in the diagnosis and management of patients with erectile dysfunction. Various agents have been studied. They include: the smooth muscle relaxants, papaverine and nitroglycerin; alpha-blockers, phenoxybenzamine and phentolamine; Calcium channel blockers such as verapamil, polypeptides, such as vasoactive intestinal polypeptides; and antidepressants such as trazodone [5], These pharmacological agents release neurotransmitters and relax the smooth muscles, resulting in decreased peripheral resistance and sinusoidal space enlargement. Amongst the various agents studied, PPV (Papaverine) is the most popular agent for the production of pharmacological erection. Papaverine HC1 is a strong nonspecific smooth muscle relaxant which acts directly on the arteries and sinusoids bypassing neurogenic influence and causes erection by relaxing the smooth muscle lining the sinusoidal channels in the corpora cavernosa allowing engorgement of the erectile bodies with blood and consequent erection [6]. Patients with poor blood flow to the cavernosal arteries of the penis experience a diminished response or no erection at all. Most men who fail to obtain full erection within approximately ten minutes after injection probably have some degree of vasculogenic impotence [7]. The injectable drug combinations of Papaverine and Phentolamine (bi-mix) and Papaverine, Phentolamine

and Prostaglandin (tri-mix) have withstood the test of time [8].

Retrospective studies have shown injection therapy to be safe and effective [9]. Liver toxicity, once a concern because of the possible association with papaverine, has become a non-issue. Scar tissue formation as a result of post-injection bleeding can be avoided with proper post-injection compression Priapism, an unwanted persistent rigid erection lasting for many hours, can be avoided with medically supervised dose-titration office visits [10]. And finally, needle size has been reduced to a user friendly 31 gauge 5/16th length. With proper instruction and medical supervision, adverse effects are practically non-existent..

Combining PPV with an alpha-adrenergic blocker further improves the erectile response. The ideal dose, drug, or combination of drugs has not yet been determined and the search for other drugs continues.[11] Like Phentolamine, Chlorpromazine is a sympathetic blocker. It is easily available in the market and is quite cheap.

The aim of our study was to determine the efficacy and safety of bimix combination of Papaverine and Chlorpromazine administered intracavernosally in patients with erectile dysfunction (ED) of various origins as compared to Papaverine alone . Few earlier studies have also shown Chlorpromazine as a useful substitute for phentolamine.

In a study by Braga, 163 patients followed for a period of 2 yrs had PGE1/Phentolamine mixture substituted for PGE1/Chlorpromazine with no difference in response in 156 [12]. In another study, 148 of 175 men (85%) responded fully to a combination of papaverine and chlorpromazine [13].

The advantage of chlorpromazine over phentolamine is that it is easily available and much cheaper. In another study by RA Uebel & AC Schmidt , the results indicate that phentolaminemesylate can effectively be replaced with an equal amount of chlorpromazine HCL in IC drug cocktails for the treatment of ED [14].

Conclusion

Papaverine-CPZ combination has proved a cheap and effective alternative to other combinations with better efficacy than Papaverine alone.

Synergism of the two drugs not only reduces the amount of individual drugs but also improves the efficacy and erection quality.There is also less incidence of penile pain, haematoma and subsequent fibrosis in long term.Prolonged erection remains the major side effect and its long term safety needs yet to be established.

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