Independent Predictive Factors for Occurrence of Ischemic Priapism after Papaverine Injection

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Purpose: To analyze the predictive factors causing ischemic priapism following penile doppler ultrasonography (PDU) with intracavernosal papaverine injection

Materials and methods: Medical records of 467 patients who underwent PDU examination following intracavernosal papaverine injection for erectile dysfunction (ED) between 2009 and 2017 were retrospectively reviewed. Patients with hematological disease anamnesis, patients taking phosphodiesterase-5 inhibitor, patients with intracavernosal injection therapy anamnesis, and patients who underwent PDU with other intracavernosal vasodilator drugs other than papaverine were excluded from the study. The remaining 268 patients were divided into two groups as priapism (38 patients) and non-priapism (230 patients). The groups were compared in terms of demographic data, American Society of Anesthesiologists (ASA) score, comorbidities, international index of erectile dysfunction (IIEF) score, and PDU results. The significant parameters were analyzed with binary logistic regression analysis. The receiver operating analysis was used to obtain cut-off, sensitivity, and specificity values for the independent predictive factors.

Results: The age, ASA score, diabetes mellitus, IIEF score, duration of ED, peak arterial, and peak end diastolic venous flow values in the 20th minute were significantly different in the two groups ($p < 0.001$). Binary logistic regression analysis found age, duration of erectile dysfunction, IIEF score, peak arterial flow, and venous flow rate in the 20th minute were predictive variables for the occurrence of priapism.

Conclusion: Young patients, patients with good IIEF score, patients with ED for a short time, and patients with normal peak arterial and venous flows are more prone to developing post-papaverine ischemic priapism.

Keywords: priapism; papaverine; prediction; erectile dysfunction

INTRODUCTION

Penile doppler ultrasonography (PDU) is performed to investigate vascular causes of ED and to detect penile cavernosal hemodynamics. For PDU, vasoactive agents such as papaverine, prostaglandin, or phentolamine are injected into the intracavernosal cavity, either alone or mixed. After injection of the vasoactive agent, the aim is to provide full erection with penile physical stimulation. Measuring peak arterial and venous flow rates allow understanding of whether the patient has a vascular problem. Peak arterial flow >35 mL/s and peak venous flow <5 mL/s excludes vascular pathologies[1]. After the PDU procedure with intracavernosal papaverine induction, if full penile erection lasts for more than 4 hours, it is evaluated as priapism. These patients generally present with painful rigid erections, while the glans penis is generally soft. Though anamnesis is sufficient for diagnosis of ischemic priapism, PDU without intracavernosal injection and aspiration of intracavernosal blood for blood gas analysis are methods used for diagnosis. On PDU if there is no flow in the intracavernosal artery and/or blood gas is PO_2 <30 mmHg, PCO2 > 60 mmHg and < 7.25 pH, ischemic priapism is confirmed. Beginning early treatment is very important to prevent permanent erection problems including necrosis and fibrosis of corpus cavernosal tissue. For treatment, conservative applications like cold compress and oral treatments (e.g., salbutamol) may be used, but the degree of evidence for these treatments is low[2].

Through the lateral proximal penile or glandulo-cavernosal route, blood is aspirated by puncturing the corpus cavernosa with an 18- or 19-gauge needle or butterfly needle. The color of the aspirated blood is generally dark and aspiration and irrigation with 0.9% NaCl continues until detumescence is obtained or fresh red blood is observed. If full detumescence is not obtained, 200 mcg/mL diluted phenylephrine is injected at 3-5-minute intervals so the full dose does not exceed 1 mg. If this treatment is not sufficient to obtain full detumescence, distal and proximal shunts are used. For ischemic priapism, the first stage of treatment of aspiration, irrigation and/or phenylephrine injection is generally sufficient. In cases with priapism lasting more than 36 hours, ED will definitely occur so the use of penis prosthesis in the same session is recommended[3].

To date, there is no data with high evidence level to predict vasoactive-agent induced ischemic priapism. If predictive factors for vasoactive agent-induced ischem-

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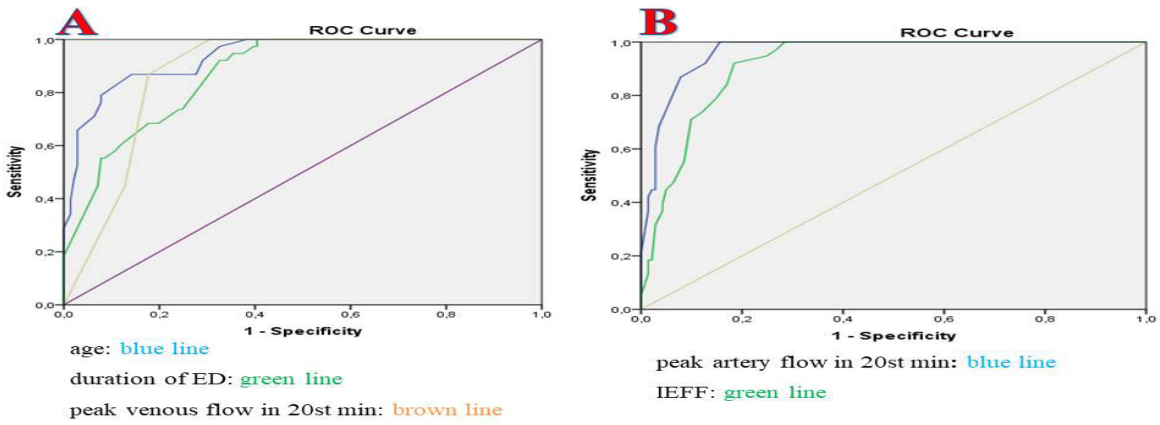

Figure 1. ROC curves for investigation of predictor variables with ischemic priapism: A) duration of erectile dysfunction and peak venous flow in the 20th minute after papaverine injection and B) IEFF score and peak arterial flow in the 20th minute after papaverine injection.

ic priapism can be identified, more suitable patients for PDU can be determined with high risk patients are closely monitored after PDU to ensure early intervention or the use of prophylactic agents.

MATERIALS AND METHODS

The study was conducted in accordance with Helsinki declarations and informed consent was obtained from the patients. Medical records of 467 patients who underwent PDU examination following intracavernosal papaverine injection for ED between 2009 and 2017 were retrospectively reviewed. Of these, patients with hematological disease, patients taking phosphodiesterase-5 inhibitor, patients with intracavernosal injection therapy, and patients who underwent PDU with intracavernosal vasodilator drugs other than papaverine were excluded from the study. The remaining 268 patients were divided into two groups as priapism (38 patients) and non-priapism (230 patients). The groups were compared in terms of demographic data, American Society of Anesthesiologists (ASA) score, comorbidities, IIEF score, and PDU results.

Patients attending the clinic for ED all had detailed anamnesis research and lipid-cholesterol-glucose profile investigation with total and free testosterone measurements obtained in the early hours of the morning. Then PDU was requested to learn whether vascular ED was present or not.

PDU procedure

For PDU, first dermal local anesthesia (with lidocaine injection) was provided to the unilateral penile lateral proximal region by the radiology department and then the corpus cavernosa was entered with a butterfly needle and a total of 40 mg papaverine injection was administered. For full erection, patients were requested to provide physical penile stimulation by hand. Peak arterial and venous flow rates were measured in the 5th, 10th, 15th and 20th minute after papaverine injection. Peak arterial and peak end diastolic venous flow measurements were measured with 7-10 mHz color pulsed realtime ultrasonography. Peak arterial flow >35 mL/s and peak venous flow < 5 mL/s were accepted as indicating sufficient and appropriate vascular system. Values other than these were evaluated as vascular ED. Patients were warned not to delay and come back to the hospital if their continued erections exceeded 4 hours, because they were discharged to their homes without waiting after the PDU procedure. Patients with painful erection lasting more than 4 hours attended the emergency service. None of these patients had conserva-

Table 1. Demographic characteristics and diagnostic features.

	Parameters Priapism (N = 38)	Non-Priapism (N = 230)	*p*
Age (years), mean ± sd	30.79 ± 6.8	46.0 ± 7.5	< 0.001
BMI (kg/m²), mean ± sd	28,0 ± 3,8	27.6 ± 3.7	.558
ASA (score), mean ± sd	1.02 ± 0.16	1.23 ± 0.4	.004
Coronary artery disease (no,%)	4 (10.5%)	19 (8.3%)	.979
DM (no,%)	5 (15.7%)	54 (23.5%)	.041
Priapism time (hour), mean ± sd (min-max)	5.02 ± 1.15 (4-8)	N/A	
IIEF score, mean±sd	24.16 ± 5.0	13.0 ± 5.7	< 0.001
Duration of ED (month), mean ± sd	16.05 ± 7.1	43.4 ± 26.1	< 0.001
Peak artery flow in 20th min. (mL/s), mean ± sd	49.8 ± 5.1	33.3 ± 7.3	< 0.001
Peak venous flow in 20th min. (mL/s), mean ± sd	0.68 ± 0.7	3.6 ± 2.2	< 0.001

Abbreviations: ASA; American Society of Anesthesia, DM; Diabetes Mellitus, IIEF; International Index Of Erectile Dysfunction, ED; Erectile Dysfunction, BMI; Body Mass Index, Sd; Standard Deviation, N/A, Not available

Table 2. Binary logistic regression analysis results of predictive and non-predictive factors.

Parameters	Odds Ratio	95% CI Lower Upper	*P*-value
Age	1.502	1.163 1.942	.002
ASA score	0.180	0.450 3.020	.280
DM	0.140	0.005 4.137	.255
Duration of ED	1.173	1.043 1.349	.008
IIEF score	0.638	0.485 0.839	< 0.001
Peak artery flow in 20th min	0.687	0.594 0.788	< 0.001
Peak venous flow in 20th min	2.283	1.963 4.061	< 0.001

tive or prophylactic priapism treatment. For 31, after skin anesthesia in the unilateral latero-proximal penile region with jetocaine, the cavernous area was entered with the aid of a butterfly needle and dark-colored blood was aspirated. For 7 patients glandulo-cavernosal entry was used. Aspiration and 0.9% NaCl intracavernosal aspiration continued until full penile detumescence was ensured. Patients without full detumescence were administered 200 mcg/mL phenylephrine at 3-5-minute intervals until full detumescence was provided. No patient was observed to have continued erection so shunt treatment was not required. To prevent hematoma below the penile skin, patients had tight penile bandaging and remained in hospital overnight and were discharged the next day. Recurrent priapism did not develop in any patient.

Statistical analysis

Using SPSS 22.0 (IBM Corp, New York, USA), variables in the groups were compared with the independent T test. Values of $p < 0.05$ were accepted as significant. Variables significant on univariate analysis were evaluated with binary logistic regression analysis. Predictive values affecting development of priapism after PDU accompanied by papaverine injection were obtained and accepted as significant with $p < 0.05$. ROC analysis was used to obtain cut-off, sensitivity, and specificity values for these predictive values. The coordinate data obtained in the ROC analysis were copied to the excel program. The line with the highest specificity value calculated with the specificity formula was determined as the cut-off value.

RESULTS

The mean follow-up periods were 14 months[6-23] and 6 months[2-12] for priapism and non-priapism groups, respectively. During this period, no patient developed ED.

Table 1 presents demographic characteristics and diagnostic features. There were no significant differences between the groups with regard to BMI and coronary arterial disease. The priapism group consisted of significantly younger patients (30.79 ± 6.8 vs 46.0 ± 7.5 years) ($p < 0.001$). The number of diabetic patients and ASA score were lower in patients with priapism. In this patient group, the IIEF score was significantly higher and the duration of ED was significantly lower than non-priapism patients. In terms of PDU parameters, patients who developed priapism had significantly higher 20th minute peak artery flow and lower 20th minute peak venous flow.

Table 2 presents binary logistic regression analysis results. Age, duration of ED, peak venous flow in 20th minute, peak artery flow in 20th min, and IIEF score were independent predictive factors in the development of priapism.

Table 3 and Figure 1A/B present sensitivity, specificity, and AUC values for independent predictive factors. Age, duration of ED, and peak venous flow in 20th minute had sensitivity and specificity of 86% to 72%, 100% to 59%, and 100% to 69%, at cut-off values of 38.5 years, 33 months, and 2.5 mL/s, respectively (**Figure 1A**). The AUC values were 0.93, 0.87 and 0.87 for age, duration of ED and peak venous flow in 20th minute, respectively. Peak artery flow in 20th minute and IIEF score had a sensitivity and specificity of 100% to 84%, and 92% to 73%, at cut-off values of 42.5 mL/s and 17.5, respectively (**Figure 1B**). The AUC values were 0.96, and 0.91 for peak artery flow in 20th minute and IIEF score, respectively.

DISCUSSION

Guidelines recommend definite intervention for priapism lasting longer than 4 hours. In ischemic priapism cases lasting >36 hours, the process progressing to necrosis and fibrosis has begun. It is recommended that penis prosthesis be used in the same session after intracavernosal drainage because of greater difficulty due to intracavernosal fibrosis in these patients[4]. Bahnasawy[5] reported that in low flow priapism >48 hours, if complete detumescence cannot be obtained in spite of treatment and clear cavernosal fibrosis occurs in patients, ED frequently develops. In a current rat model, Cınar et al.[6] reported that in an ischemic priapism, the anti-inflammatory, antifibrotic and antioxidant molecule, pirfenidone, reduces cavernosal fibrotic activity and maintains erectile function.

Priapism is divided to ischemic and rapid flow/nonischemic variants. In clinical practice, ischemic priapism is observed at rates of about 95%. Priapism occurring after intracavernosal drug-induced erection generally has ischemic character. Ischemic priapism is a full painful erection of the penis. The glans is generally soft, the corpus cavernosa is rigid and is not flexible with compression on examination. The aspirated fluid has acidic, hypercapnic, and hypoxic findings on blood gas investigation. Penile Doppler USG identifies no intracavernosal arterial flow and venous return, different

Table 3. ROC curve analysis for independent predictive factors.

	cut-off	AUC	sensitivity	specificity	95% CI lower upper
Age	38.5	0.935	0.868	0.727	0.897 0.973
Duration of ED	33.0	0.871	1.000	0.596	0.818 0.924
Peak venous flow in 20th min	2.5	0.876	1.000	0.695	0.826 0.925
Peak artery flow in 20th min	42.5	0.964	1.000	0.844	0.940 0.987
IIEF score	17.5	0.916	0.921	0.737	0.876 0.925

from nonischemic priapism[7].

PDU is frequently used for ED diagnosis in clinics and is a radiological test that directs treatment and is irreplaceable. To continue to use PDU, at the same time we wish to prevent the occurrence of the unwanted complication of ischemic priapism. If we have clinical predictors for ischemic priapism after papaverine injection, the formation of priapism may be prevented or early intervention performed or prophylactic treatment can be attempted. If we can obtain the drug, the use of PGE1 instead of papaverine can lower the risk of ischemic/low-flow priapism development after PDU to < 1%[8].

Shamloul[9] reported that rigid erection continuing 1 hour after papaverine injection and lack of observation of intracavernosal arterial flow on color Doppler USG predicted priapism with 100% specificity and sensitivity.

Metawea[10] reported peak arterial flow > 66 mL/s and peak venous flow < 5 mL/s at the end of 1 hour predicted priapism. We evaluated our patients at the end of the 20th minute as a clinical standard. Peak arterial flow > 42.5 mL/s and venous flow < 2.5 mL/s in the 20th minute as cut-off values were identified to have predictive value for priapism development. These PDU values determine patients with vascular sufficiency. Papaverine-induced priapism is observed more in patients without vascular problems. In the literature, we did not encounter any other study researching the correlation between 20th minute PDU values and priapism. Prospective and large-series studies performed on this topic in the future will confirm our predictive data and cut-off values and increase reliability.

Lomas[11] reported higher rates of papaverine-induced priapism in young males with better basal erectile functions. Kılıç[7] identified 2.68% priapism in PDU patients induced with 60 mg intracavernosal papaverine and reported men with priapism were younger compared to those without priapism. Rajmil[12] reported papaverine-induced priapism rates after PDU of 5.05% and that age was not a predictive factor. In our study, we found the cut-off value for the development of priapism was 38.5 years. We identified that priapism after PDU (papaverine-induced erection) was observed more often in patients younger than this age. In our study, we identified that papaverine-induced iatrogenic priapism occurred more often in young males with psychogenic erection causes and a low possibility of vascular pathologies.

In an article researching whether there were correlations between papaverine-induced priapism and IIEF, Erectile Function Domain Score (IIEF-EF), and Erection Hardness Score (EHS), Sönmez[13] reported that the prevalence of priapism increased in young males with high IIEF-EF and EHS scores and patients with low vascular comorbidity rates. In our study, the IIEF score obtained before PDU had predictive value for papaverine-induced priapism and we identified the cut-off value as 17.5. In priapism patients, IIEF score was 24.16, while in the nonpriapism group it was 13.0 ($p < 0.001$). We think the better IIEF score in priapism patients is because most patients being young and had only psychogenic causes underlying erection etiology.

The duration for erection problems before attending the clinic was mean 16.5 months in the priapism group and mean 43.4 months in the nonpriapism group ($p < 0.001$). In the literature, we did not encounter any study researching the correlation between erection duration and priapism. Patients in the priapism group were younger and had greater sexual activity and anxiety which might have led them to attend the clinic earlier.

The largest limitation of our study is the retrospective nature. Another limitation is the low number of patients in the priapism patient group. We recommend prospective and large participation studies be performed to evaluate the results obtained in this study.

CONCLUSIONS

In conclusion, priapism after papaverine-induced PDU is frequently encountered in clinical practice and is an unwanted complication. If patients with greater probability of priapism development after PDU can be predicted, it appears more logical to skip the PDU test, to use prophylactic medication, to monitor these patients in clinics or to use PGE1 instead of papaverine. Priapism after PDU is more common in patients under the age of 38.5, erection problems lasting less than 33 months, IIEF score < 17.5, 20 minutes peak artery flow> 42.5 mL / s, and peak tip diastolic flow rate < 2.5 mL / s in patients with eruption stimulated with papaverine.

REFERENCES

1. J E halls, D V Patel, M Walkden, U Patel. Priapism: pathophysiology and the role of the radiologist. The british journal of radiology. 2012;85:579-585.
2. Mohamad Habous, Mohammed Elkhouly, Osama Abdelwahab, Mohammed Farag, Khaled Madbouly. Noninvasive treatments for iatrogenic priapism: Do they really work? A prospective multicenter study. Urol Ann. 2016;8:193-6.
3. F Martinez Portillo, J Hoang-Boehm, J

Weiss, P Alken, K Jünemann. Methylene blue as a succesful treatment alternative for pharmacologically induced priapism. Eur Urol. 2001;39:20-3.

4. Salonia A, Eardley I, Giıliano F et al. European Association of Urology guidelines on priapism. Eur Urol. 2014;65:480-9.
5. MS El-Basnassawy, A Dawnood, A Farouk. Low-flow priapism: Risk Factors for erectile dysfunction. BJU İnt. 2002;89:285-90.
6. Cinar, O., Bolat, M.S., Erdem, S. et al. The effect of an antifibrotic agent, pirfenidone, on penile erectile function in an experimental rat model of ischemic priapism. Int J ImpotRes. 2019; (Epub ahead of print)
7. M Kılıç, EC Serefoğlu, A T Ozdemir, MD Balbay. The actual incidence of papaverin-induced priapism in patients with erectile dysfunction following penile colour doppler ultrasonography. Andrologia. 2010;42:1-4
8. R Seyam, K Mohamed, A Al Akhras, H Rashwan. A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E1. Int J Impot Res. 2005;17:346-53.
9. R Shamloul, H M Ghanem, A Salem, I I Kamel, A A Mousa. The value of penile duplex in the prediction of intracavernous drug-induced priapism. İnt J İmpot Res. 2004;16:789.
10. Bahgat Metawea, Abdel-Rahman El-Nashar, Amr Gad-Allah, Mazen Abdul-Wahab, Rany Shamloul. İntracavernous Papaverine/ Phentolamine induced priapism can be accurately predicted with color doppler ultrasonograhy. Urology. 2005;66:858-60.
11. G M Lomas, J P Jarow. Risk factors for papaverine-induced priapism. J Urol. 1992;147:1280-1.
12. O Rajmil, F Garcia, E Fabian, L Bassas, JM Pomerol. Prolonged erections after diagnostic injection of papaverine chlorhydrate. Arch Esp Urol. 1991;44:179-82.
13. Mehmet Giray Sönmez, Ahmet Öztürk. İs there a relation between priapism occurring after penile doppler ultrasonography and international erectile function index score and erection hardness score levels? Turk J Urol. 2017;43:439-743.