

# Inhibitory Effect of Silodosin, Tamsulosin and Terazosin in Phenylephrine Induced-Prostate Smooth Muscle Contraction (a Comparative *in vitro* Study)



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## Abstract

**Objective:** This *in vitro* study aims to compare the inhibitory effect of those  $\alpha$ -blocker to the phenylephrine induced prostate smooth muscle contraction.

**Research Method:** Twenty eight eligible BPH patients were randomly allocated to 4 groups which are one control group (without  $\alpha$ -blocker therapy) and 3 intervention groups treated with silodosin, tamsulosin and terazosin for 7 days prior to TURP surgery. The prostate tissue samples were taken during TURP surgery. This sample prepared on organ bath containing thyroid liquid and further induced with phenylephrine at dose 10-4  $\mu$ g/ml to measure its contraction. A one-way ANOVA analysis was performed to investigate the significant difference among groups.

**Result:** The mean contraction result in control, silodosin, tamsulosin and terazosin groups were 7,798mV, 1,718mV, 3,416mV, and 5,956 mV respectively (Table 1). There was a significant difference in contraction value among 4 groups ( $p=0,000$ ). The silodosin treatment group had the lowest mean contraction value against the controls compared with the tamsulosin and terazosin groups.

**Conclusion:** Silodosin has the strongest inhibitory effect in phenylephrine-induced prostate smooth muscle contraction in the *in vitro* study.

**Keywords:** Antagonists; Adrenoceptors; Urinary Tract; Cardiovascular system; Silodosin; Tamsulosin; Prazosin; Terazosin; Necrotic; Phenylephrine

**Abbreviations:** LUTS: Lower Urinary Tract Symptoms; BOO: Bladder Outlet Obstruction; IP3: Inositol Triphosphate; DAG: Diacylglycerol

## Introduction

BPH is a chronic progressive disease associated with lower urinary tract symptoms (LUTS) which its prevalence increases with age and reduces the quality of life in elderly male [1,2]. Treatment for BPH aims to relieve two types of urinary tract obstruction: mechanical urinary tract obstruction caused by tissue compression due to an enlarged prostate and functional urinary tract obstruction caused by constriction of the urinary tract and prostatic smooth muscle via sympathetic  $\alpha$ 1 adrenoceptors ( $\alpha$ 1-AR). As a result,  $\alpha$ 1-AR antagonists are widely recognized as the first-line pharmacotherapy for BPH treatment [3]. Several  $\alpha$ 1-AR antagonists with its difference of selectivity are available for treatment of this disease, including silodosin, tamsulosin and terazosin. Many studies showed that those  $\alpha$ -blocker seem to have similar efficacy in improving symptoms and urinary flow rates [4]. The high selectivity of the  $\alpha$ 1-adrenergic receptor antagonist has great efficacy and is associated with minimal side effect on cardiovascular system. Based on study that was conducted on hamsters, silodosin has a very high selectivity up to 38 times compared with tamsulosin. Another study on *in vivo*

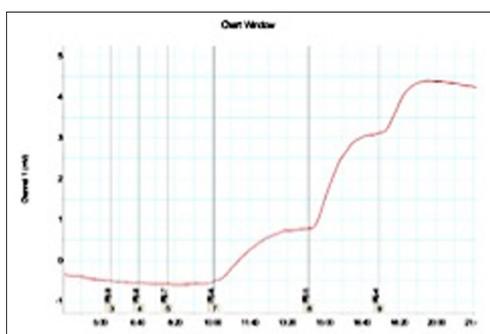
animal test subject that compared silodosin, tamsulosin, and prazosin concluded that silodosin showed the highest selectivity compared with tamsulosin and prazosin [5].

Previous *in vitro* study has shown that long term treatment of  $\alpha$ -adrenergic receptor antagonists (tamsulosin 0,4mg once daily) in BPH patient can increase phenylephrine-induced prostate smooth muscle contraction [6]. This is probably due to a supersensitization mechanism in long term treatment. It is not yet clear, however, whether the use of adrenergic receptor antagonists in BPH in a short period of time can affect the contraction of smooth prostate smooth muscle. On short term crossover study comparing several types of alpha blockers, showed that 7 days treatment of alpha blocker was sufficient to determine its effectiveness and efficacy. Clinical research also suggests that different types of alpha blockers having different selectivity and affinity have similar effectiveness on improving symptoms of IPSS and urinary outflow on BPH patient [4]. The differences in selectivity and affinity from each alpha blocker allegedly have different effects on the prostate

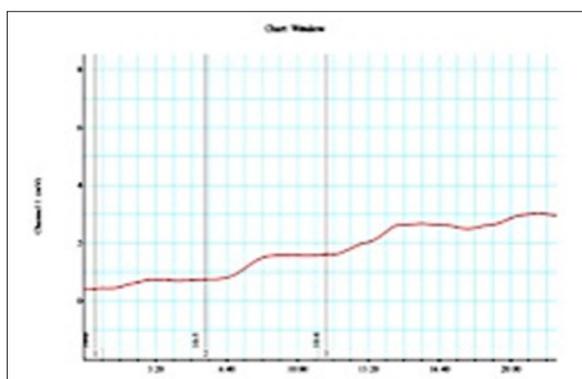
smooth muscle contractility. Therefore, research that compare the inhibitory effect of several alpha blocker against prostate smooth muscle contraction is needed.

## Methods

Twentyeight eligible BPH patients having indication for surgical management were randomly allocated to 4 groups which are one control group (without  $\alpha$ -blocker therapy) and 3 intervention groups treated with silodosin, tamsulosin and terazosine for 7 days prior to TURP surgery. Key exclusion criteria were previous alpha blocker treatment, suspicious for prostate malignancy and patient with diabetes mellitus. The specimen was immediately transported in cold, oxygenated tyrod's solution ( $p^H$  7,4) (composition: 135NaCl; 5 KCl; 2,5 CaCl<sub>2</sub>; 1,3 MgSO<sub>4</sub>; 1,2 KH<sub>2</sub>PO<sub>4</sub>; 20 NaHCO<sub>3</sub>; 10D-Glucose) to the laboratory. Prostate specimen were kept in aerated tyrod's buffer (95% oxygen and 5% carbon dioxide) at a constant temperature of 37°C while they were cut and separated from surrounding necrotic burned tissue part and further prepared in organ bath containing aerated tyrod's buffer (37°C) between stainless steel hangers. The prostate specimen were attached to force displacement transducers and the tension was displayed on a polygraph.



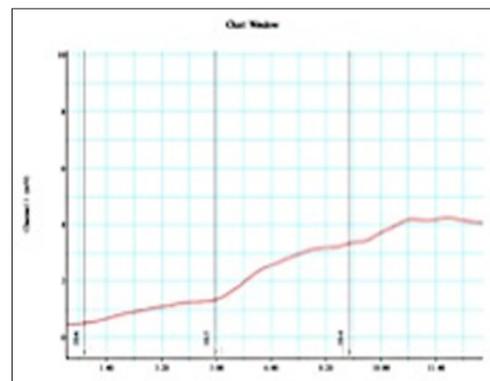
**Figure 1:** Graphic of prostate smooth muscle contractility in the power Lab tool with MLSO2 software from control group patients (patient Mr.B). In this graph also shows that contraction start at exposure dose 108ug/ mL phenylephrine. The optimal phenylephrine is 108.



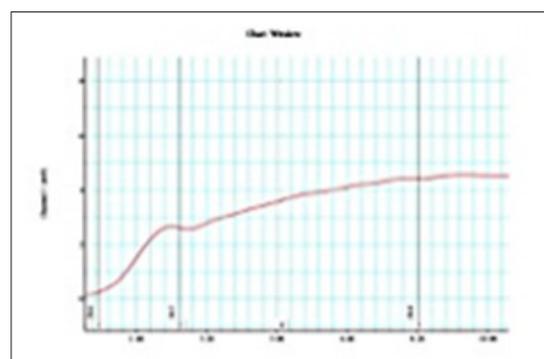
**Figure 2:** Graphic of prostate smooth muscle contractility on power Lab device using software from silodosin sample group. (patient Mr.T).

The signal of the pressure was digitized using the powerlab software program (ADInstruments, Bella Vista, NSW, Australia). The LabChart Software Package (ADInstruments) on a computer (DELL) was used for continuous data acquisition and

the subsequent analysis. The tension was set at 0,5g. The tissues were allowed to equilibrate in tyrod's buffer for 2 hours. After the 2-hour equilibration period, the tissue bath content was applied with 10-4 $\mu$ g/mL phenylephrine as exogen agonist to induced tissue contractility. The contractility values of all specimens was displayed on polygraph (Figures 1-4) recorded in millivolt(mV) and then analyzed using onewayanova test.



**Figure 3:** Graphic of prostate smooth muscle contractility on power Lab device using chart MLSO23 software from Tamsulosin sample group. (patient Mr.AW).

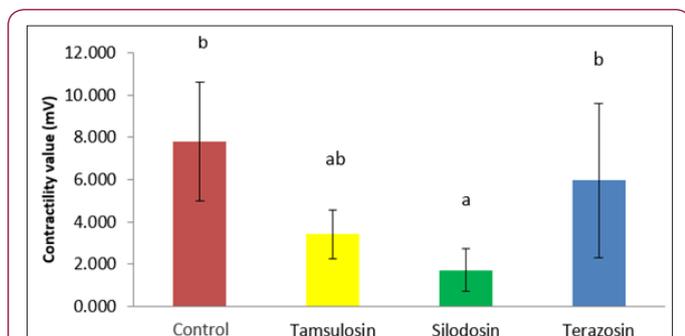


**Figure 4:** Graphic of prostate smooth muscle contractility on power lab device using chart MLSO23 software from Terazosin sample group. (Patient Mr.J).

## Results

The result of the prostate smooth muscle contractility test using the bath organ instrument with phenylephrine exposure dose of 10-4  $\mu$ g/mL showed significantly different ( $p < 0.05$ ) between control group compared to silodosin, tamsulosin, terazosin groups and, as shown in Table 1. Terazosin group had the highest mean contraction value compared to tamsulosin and silodosin group against control group. Silodosin group had lowest mean contraction value rate compared to tamsulosin and terazosin group against control group. The prostate contractility response in all four groups with phenylephrine dose exposure of 10-4 $\mu$ g/mL were analyzed using oneway anova. The result of oneway anova analysis was presented in Table 2. One way ANOVA test results of contractility value from control, silodosin, tamsulosin, terazosin group with phenylephrine dose exposure 10-4 $\mu$ g/mL showed sig value 0.000  $< 0.05$ , so it can be concluded that there is difference of prostate smooth muscle contraction value from sample that was obtained from patient control group, and groups that received silodosin,

tamsulosin, terazosin therapy after exposed with a dose 10-4 $\mu$ g/mL of phenylephrine. Post Hoc Tukey Test are presented in Figure 5. The lowest contraction value was found in the group treated with silodosin and when compared between other treatment groups and control, the silodosin group had significant difference value compared with control group. There are no significant difference between tamsulosin and terazosin group compare with control group.



**Figure 5:** Post Hoc Tukey analysis of phenylephrine-induced prostate smooth muscle contraction from control, silodosin, tamsulosin and terazosin group.

**Table 1:** Mean values of Phenylephrine-induced prostate smooth muscle contractility.

Groups	Mean Contractility (mv)	Stdev	p
Control	7.798	2.789	0,000
Tamsulosin	3.416	1.155	
Silodosin	1.718	1.009	
Terazosin	5.956	3.647	

**Table 2:** One way ANOVA analysis result of phenylephrine induced prostate smooth muscle contractility among groups.

Variable	Sum of square	df	Mean Square	F	Sig.
Between groups	11.274	3	3.758	9.307	.000
Within groups	9.639	24	.402		
Total	20.912	27			

## Discussion

One of the LUTS symptoms pathophysiology in BPH patients is increased in smooth muscle tone of the prostate. Selective  $\alpha$ 1-adrenergic receptor antagonist is chosen as a therapy for BPH because it is effective and safe for long-term use [7-10]. These drugs act on the dynamic component of Bladder Outlet Obstruction (BOO), that reduce smooth muscle tone of the prostate and bladder neck [11]. Prostate smooth muscle contraction caused by stimulation of the adrenergic receptor by noradrenaline agonist. After ligand (adrenergic agonists) bind to the receptor, membrane phospholipids undergo hydrolysis through phospholipase C- $\beta$ , resulting in a second messenger inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). Furthermore IP<sub>3</sub> binds to IP<sub>3</sub> receptor on endoplasmic reticulum calcium ions resulting in excretion of Calcium (Ca<sup>++</sup>) into the cytoplasm, whereas DAG together with

calcium activates the enzyme protein kinase C- $\alpha$  and subsequently leads to phosphorylation of several intracellular proteins. In addition, activation of this enzyme causes the opening of calcium channels in the plasma membrane that is sensitive to nifedipine (L-type Ca<sup>++</sup>channel) that causes more extracellular calcium slide into intracellular.

This calcium binds to calmodulin forming Ca-calmodulin which then causes contraction of the smooth muscle of the prostate [12]. In this invitro contractility studies indicate that the prostate smooth muscle contraction occurred after administration of phenylephrine as an exogenous  $\alpha$ -adrenergic agonist. It concludes that there is a binding process between phenylephrine as an agonist with  $\alpha$ -adrenergic receptor that led to the contraction of prostate smooth muscle. When the  $\alpha$ -adrenergic receptor antagonist binds to the adrenergic receptor, receptor activation and intracellular signaling generation were blocked. The  $\alpha$ -adrenergic receptor antagonists bind to the same site as the  $\alpha$ -adrenergic agonist that inhibits ligand binding (adrenergic agonist) with the receptor in a competitive [13,14]. In this study, when phenylephrine given on prostate smooth muscle tissue with prior  $\alpha$ -adrenergic antagonist therapy resulting lower value of smooth muscle contraction compared with patients without  $\alpha$ -adrenergic antagonist therapy. It also demonstrates that antagonists of  $\alpha$ -adrenergic is still bind with  $\alpha$ -adrenergic receptor on apart smooth muscle tissue of the prostate, so the contractility value of the prostate smooth muscle was inhibited.

In human tissue there are three subtypes of adrenergic  $\alpha$ 1-receptor, three of them are  $\alpha$ 1A,  $\alpha$ 1B, and  $\alpha$ 1D. Adrenergic  $\alpha$ 1A-subtype located in the prostate tissue, bladder base, bladder neck, prostatic capsule and prostatic urethra, have a role in the contraction of the smooth muscle of the prostate [15,16].  $\alpha$ 1A receptor subtype have 70% proportion of the population from  $\alpha$ 1 adrenergic receptors [17,18]. In prostate that undergo hyperplasia, the ratio of subtypes  $\alpha$  1A,  $\alpha$ 1B and  $\alpha$ 1D by 85: 1: 14 in contrast to the normal prostate, which amounted to 63: 6:31 [19]. Nowadays, there is wide range of adrenergic receptor antagonist drugs ranging from the nonselective to selective subtype group. Silodosin has the highest selectivity when compared with tamsulosin and terazosin. Mentioned that silodosin has a higher selectivity 1400 times than terazosin and 40 times higher than with tamsulosin [5]. This study showed that administration of  $\alpha$ -adrenergic receptor antagonists for 7 days in BPH patients may decrease the response of prostate stromal smooth muscle contraction after exposure of exogenous  $\alpha$ -adrenergic receptor agonists in the invitro study. Additionally, the data showed that the mean contraction values of prostate tissue obtained from patient treated  $\alpha$ -adrenergic receptor antagonist silodosin, tamsulosin, terazosin for 7 days prior to surgery were significantly different ( $p < 0.001$ ).

Silodosin has the stronger inhibitory effect of prostate smooth muscle contraction compare with tamsulosin and terazosin. Mean contractility values from silodosin group was significantly lower compared with control group and terazosin group. In silodosin group also has a lower mean contractility value (statistically not significant) compared with tamsulosin group. The difference of inhibitory effects in this study were related to

differences in selectivity of these three  $\alpha$ -adrenergic antagonists. This research show that the highest selectivity of  $\alpha$ -adrenergic receptor antagonists will provide better inhibitory effect in phenylephrine-induced prostate smooth muscle contraction. The development of uroselective  $\alpha$ -blockers with increased affinity for the  $\alpha$ 1A-adrenergic receptor over other subtypes has provided the possibility to maximize efficacy [20,21]. In contrast with many clinical research studies said that silodosin, tamsulosin and terazosin have the same effectiveness in improving the symptoms of IPSS and urinary emission rate of BPH patients. Tamsulosin have the same effectiveness in improving complaint LUTS compared with terazosin [22]. Other clinical research also mentioned that silodosin has the same effectiveness in improving the symptoms of LUTS compared with tamsulosin [23].

## Conclusion

There is a significant difference in phenylephrine induced prostate smooth muscle contraction value among silodosin, tamsulosin and terazosin group. Silodosin has the strongest inhibitory effects in phenylephrine induced prostate smooth muscle contraction in the invitro study. This study could be one of the basic theory of the use of  $\alpha$ -adrenergic receptor antagonists for the treatment of BPH.

## Suggestions

More research is needed to determine the effect of  $\alpha$ -adrenergic receptor antagonist on the contractility of the prostate with more varied range of provision from 1 week, 2 weeks and 4 weeks in order to be the basis for consideration and the protocol for administration of antagonists adrenergic receptor- $\alpha$  in patients with BPH. More research is needed to prove that differences in selectivity and affinity of various types of receptor- $\alpha$  adrenergic antagonist related to its potential in reducing prostate contractility.

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