Original Article - Lower Urinary Tract Dysfunction

Investig Clin Urol 2020;61:600-606.
https://doi.org/10.4111/icu.20200053
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY

Efficacy and safety of dose escalation in male patients with overactive bladder showing poor efficacy after low-dose antimuscarinic treatment: A retrospective multicenter study

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Purpose: To analyze the efficacy and safety of standard-dose antimuscarinic treatment on male patients with overactive bladder (OAB) symptoms showing poor efficacy after low-dose antimuscarinics.

Materials and Methods: We retrospectively reviewed the data of 566 male patients aged ≥40 with OAB symptoms between January 2017 and June 2018. They were treated with low-dose antimuscarinics for at least 4 weeks and showed poor efficacy; therefore, they were switched to standard dose antimuscarinic treatment (5 mg of solifenacin) for ≥12 weeks. The international prostate symptom score (IPSS) and overactive bladder symptom score (OABSS) at baseline (V0), 4 weeks (V1), and 12 weeks (V2) were analyzed. Post void residual urine volume (PVR) was also recorded.

Results: The median age, body mass index, and prostate-specific antigen levels were 69.0 years, 24.2 kg/m^2, and 1.24 ng/dL, respectively. The mean value of the total IPSS and OABSS significantly decreased between V0 and V2 (from 16.73 to 13.69 and 7.33 to 5.34, respectively, all p<0.001). All component scores from each questionnaire demonstrated a significant decrease except for numbers three and six on the IPSS questionnaire. PVR was increased from V0 to V2 (36.40 to 68.90 mL, p=0.015). Four and nine patients experienced constipation and thirst, respectively, and all adverse effects were graded as ≤2.

Conclusions: Standard dose antimuscarinic treatment using solifenacin (5 mg) may be a safe and effective treatment for patients with OAB symptoms refractory to low-dose antimuscarinic treatment.

Keywords: Muscarinic antagonists; Prostatic hyperplasia; Treatment outcome; Urinary bladder, overactive

Received: 14 February, 2020 • **Revised:** 21 April, 2020 • **Accepted:** 11 June, 2020 • **Published online:** 18 September, 2020
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INTRODUCTION

In 2002, the International Continence Society defined overactive bladder (OAB) as the presence of urgency, regardless of urge incontinence, usually accompanied by urinary frequency and nocturia [1]. Although there are insufficient data on OAB prevalence according to this definition, OAB may occur in any age group; similar incidence rates are observed in males and females, with a tendency to increase with age [2]. A European research group reported that 16.6% (15.6% males and 16.4% females) of the population aged ≥40 years demonstrated OAB symptoms [3] and similar results were reported by a study in the United States [4]. These studies indicate that a significant proportion of the adult population appears to be suffering from OAB symptoms that may lower daily quality of life (QoL). Previous studies have reported that the influence of OAB on QoL may be greater than that of diabetes mellitus [5,6], and patients with OAB may have difficulties in interpersonal relationships and have a higher risk of depression than controls [7,8]. In addition, the risk of falling down and related fractures is 30% higher in patients with OAB than in those without OAB [9].

Although it is known that both male and female patients may share similar OAB pathophysiology [3], elderly male patients may particularly suffer from OAB symptoms attributable to degeneration of bladder function caused by bladder outlet obstruction. This is due to benign prostatic hyperplasia (BPH), which increases with age [10]. Therefore, while OAB is more common in female than in male patients in their 40s, the incidence rapidly increases in male patients in their 50s and reaches similar levels or becomes even more common in male than female patients in their 60s [11]. In male patients with OAB concurrent with BPH, α-blocker monotherapy or α-blocker plus low-dose anticholinergic combination therapy is often preferred instead of administering a standard dose of anticholinergics, because of the possibility of encountering acute urinary obstruction and increased amount of residual urine. However, with low-dose anticholinergic treatment, patients frequently experience unsatisfactory improvements of their symptoms related to OAB, such as frequency, urgency, and nocturia, making it difficult to improve overall lower urinary tract symptoms (LUTS).

In this study, we therefore aimed to investigate the clinical efficacy and safety of standard dose antimuscarinic treatment on male patients with OAB symptoms who showed poor efficacy after low-dose antimuscarinic treatments by reviewing symptom scores recorded throughout the study period.

MATERIALS AND METHODS

1. Patients and inclusion/exclusion criteria

The protocol of this study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki and was approved by the Institutional Review Board Committee for Human Subjects at Hallym University Hospital (approval number: 2016-I011). The requirement for written informed consent was waived due to the retrospective nature of the study. The sponsors of this study were not involved in conducting the study in any way, including its design, data collection, data analysis or interpretation or writing the report. This study was conducted of 1,150 patients with OAB symptoms between January 2017 and June 2018. A total of 566 patients with LUTS including OAB symptoms (both voiding and storage symptoms) who visited outpatient clinics and undergoing pharmacologic therapy were included in this study. Inclusion criteria were men of ≥40 years of age showing poor efficacy in OAB symptoms improvement after at least 4 weeks of low-dose antimuscarinic treatment (propiverine, 10 mg or tolterodine, 2 mg) [12]. Due to this, treatment was changed to standard dose antimuscarinic treatment [13] using solifenacin (5 mg) for more than 12 weeks. 'Poor efficacy' was defined as a total overactive bladder symptom score (OABSS) of ≥3, and/or ≥2 points in the OABSS questionnaire number 2 with the reference to the definition of OAB [14]. All patients included in the analysis were able to answer to each questionnaire required for the study. Exclusion criteria were patients being changed to an α-blocker and/or 5α reductase inhibitor regimen during the study period, previous history of acute urinary retention (AUR), urethral stricture, moderate to severe liver and/or renal disease, bladder cancer, prostate cancer, neurogenic bladder, interstitial cystitis, urinary tract infections, urinary tract stones, previous radiation of the pelvis, and other current or past malignancies of the pelvic organs.

2. Outcome measurement

Baseline evaluations included a detailed medical and medication history, physical examination, urinalysis, and blood tests including total serum prostate-specific antigen levels. All eligible patients showing poor efficacy after low-dose treatment were prescribed a standard dose antimuscarinics (solifenacin, 5 mg) as they were enrolled in the study. Both international prostate symptom score (IPSS) and OABSS were recorded at the patients' first visit of enrolment (V0), and after 4 (V1) and 12 weeks (V2) of solifenacin (5 mg) therapy. The changing trend of the mean values for the total and for each component of the IPSS and OABSS

questionnaires (Q1–Q7 and a QoL questionnaire for IPSS, and Q1–Q4 for OABSS) throughout the study period was analyzed. Because post void residual urine (PVR) was not checked in all patients, or the timing of the measurement was not constant among the patients, we included the PVR records at V0, V1, and V2 in only 323 patients. In addition, adverse drug reactions were monitored at all visits and the seriousness or severity was recorded according to the common terminology criteria for adverse events version 4.0 (CTCAE ver. 4.0). Intervention with respect to adverse effects, along with any association with solifenacin therapy, was also described.

3. Statistical analysis

Continuous variables are represented as median values, and interquartile ranges were calculated for each variable. Differences in the mean IPSS and OABSS between V0 and V1 or V0 and V2 were analyzed using paired Student t-test. Changes in the mean IPSS and OABSS from V0 (baseline) to V1 or V2 were analyzed using mixed-model repeated measures as *post hoc* analyses. All statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA); all tests of significance were two-tailed and p-values <0.05 were considered statistically significant.

Table 1. Patient demographics and clinical characteristics

Variable	Median (IQR)
Age (y)	69.0 (60.0–75.0)
BMI (kg/m^2)	24.2 (22.4–25.7)
PSA (ng/dL)	1.24 (0.49–2.64)
IPSS total	15.0 (10.0–22.0)
IPSS-QoL	3.0 (3.0–4.0)
OABSS total	6.0 (4.0–8.0)
OABSS Q2 (nocturia)	3.0 (2.0–5.0)
OABSS Q3 (urgency)	2.0 (2.0–4.0)

IQR, interquartile range; BMI, body mass index; PSA, prostate-specific antigen; IPSS, international prostate symptom score; IPSS-QoL, IPSS-quality of life; OABSS, overactive bladder symptom score.

RESULTS

The median age, body mass index, serum PSA levels, and total IPSS and OABSS of the 566 patients were 69.0 years, 24.2 kg/m^2, 1.24 ng/dL, and 15.0 and 6.0 points, respectively (Table 1). The average duration of low-dose anticholinergic treatment before enrolment was 23.1 (range, 4–312) weeks.

All questions in the IPSS questionnaire relating to storage symptoms (Q2, 4, and 7) and some questions relating to obstructive symptoms (Q1 and 5), along with the QoL and IPSS total score, showed significant improvement; conversely, Q3 and 6, questions relating to intermittency and straining, respectively, showed no significant improvement during the study period (Fig. 1A). Regarding the OABSS questionnaire, all four questions and the total OABSS revealed significant improvement over the study period (Fig. 1B). For questions related to obstructive symptoms which showed an improvement in IPSS (Q1, Q3, and 5), only the scores of V2 demonstrated a significant decrease compared with those of V0 (p<0.001 [Q1], p=0.030 [Q3], and p<0.001 [Q5]), whereas those of V1 were not statistically significant compared with

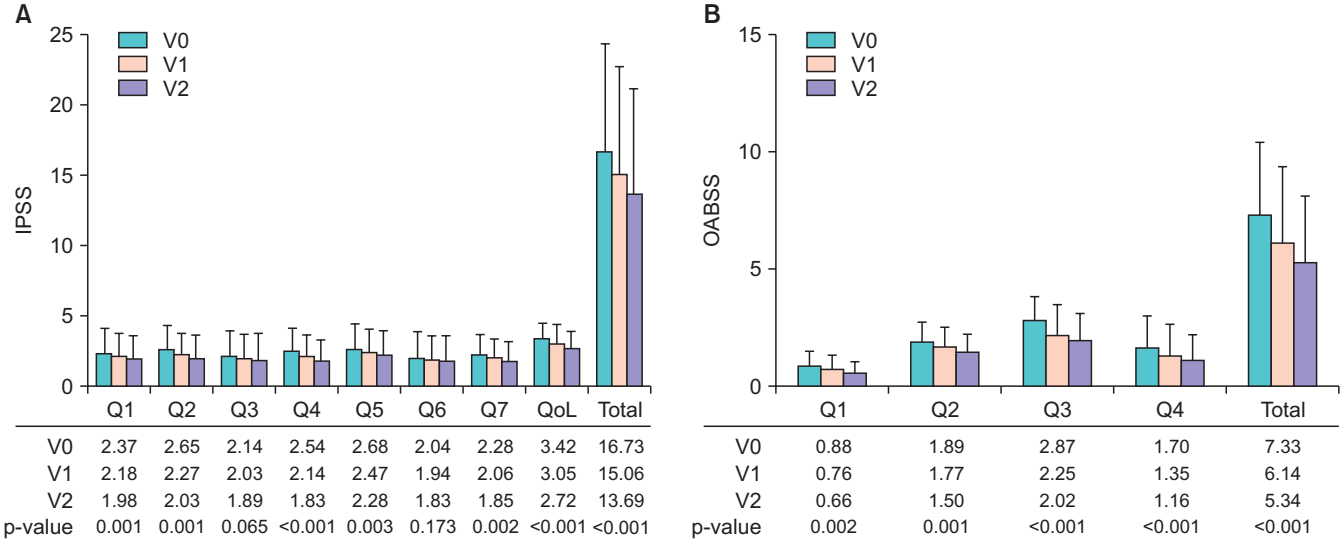

Fig. 1. Mean values of scores recorded at baseline (V0), 4 weeks (V1), and 12 weeks (V2) after initiation of solifenacin (5 mg) therapy. (A) International prostatic symptom score (IPSS). (B) Overactive bladder symptom score (OABSS). All p-values are from mixed-model repeated measures. QoL, quality of life.

https://doi.org/10.4111/icu.20200053

Table 2. Changes in IPSS and OABSS from baseline (V0) to 4 (V1) and 12 (V2) weeks after initiation of solifenacin (5 mg) therapy

Change in the IPSS and OABSS	V0 to V1	p-value	V0 to V2	p-value
Mean change (Δ) in the IPSS from V0 to V1 or V2				
Question 1 Incomplete emptying	-0.186	0.083	-0.395	<0.001
Question 2 Frequency	-0.379	<0.001	-0.626	<0.001
Question 3 Intermittency	-0.111	0.341	-0.252	0.030
Question 4 Urgency	-0.398	<0.001	-0.710	<0.001
Question 5 Weak stream	-0.214	0.055	-0.403	<0.001
Question 6 Straining	-0.105	0.386	-0.224	0.062
Question 7 Nocturia	-0.222	0.014	-0.439	<0.001
Quality of life	-0.368	<0.001	-0.707	<0.001
Total	-1.663	0.003	-3.046	<0.001
Mean change (Δ) in the OABSS from V0 to V1 or V2				
Question 1 Frequency	-0.119	0.008	-0.222	<0.001
Question 2 Nocturia	-0.139	0.022	-0.387	<0.001
Question 3 Urgency	-0.612	<0.001	-0.845	<0.001
Question 4 Urge Incontinence	-0.349	0.001	-0.544	<0.001
Total	-1.197	<0.001	-1.200	<0.001

IPSS, international prostatic symptom score; OABSS, overactive bladder symptom score.

Table 3. Number of patients showing improvement, no change, or aggravation of IPSS and OABSS and comparing at baseline to 12 weeks of solifenacin (5 mg) therapy (n=566)

Change in symptom	IPSS		OABSS	
	IPSS Q4	IPSS total	OABSS Q3	OABSS total
Improved	309 (54.6)	405 (71.6)	342 (60.4)	400 (70.7)
No change	196 (34.6)	47 (8.3)	177 (31.3)	95 (16.8)
Aggravated	61 (10.8)	114 (20.1)	47 (8.3)	71 (12.5)

Values are presented as number (%).
IPSS, international prostatic symptom score; OABSS, overactive bladder symptom score.

those of V0 (p=0.083 [Q1], 0.341 [Q3], and 0.055 [Q5]) (Table 2). On the contrary, all questions related to storage symptoms (Q2, 4, and 7) in IPSS and all four questions in the OABSS recorded at either V1 or V2 showed significant improvements compared with V0 (Table 2). Overall, 54.6% and 71.6% of patients showed improvements with respect to Q4 (related to urgency) and total IPSS respectively, whereas 60.4% and 70.7% of patients showed improvements with respect to Q3 (related to urgency) and total OABSS, respectively (Table 3).

In 323 patients who had records on PVR, the mean PVR at V0, V1, and V2 was 36.40±98.85, 66.45±102.7, and 68.90±118.3 mL, respectively (Fig. 2). Among the total of 566 patients, nine and four patients experienced thirst and constipation, respectively. For those who complained of thirst, none required intervention and were graded 1 according to CTCAE

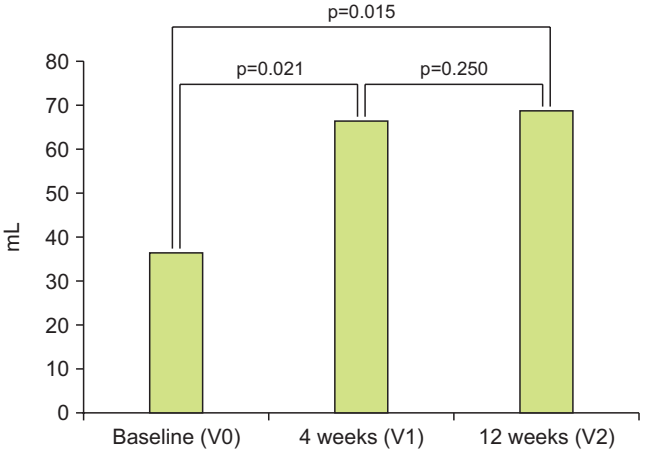

Fig. 2. Mean values of postvoid residual urine volume at baseline (V0), 4 weeks (V1), and 12 weeks (V2) after initiation of solifenacin (5 mg) therapy.

ver. 4.0. However, for those who complained of constipation, one patient was administered with magnesium sulfate, and was therefore graded 2. No patients showed serious adverse events necessitating procedures, such as catheterization to manage AUR. All patients enrolled in the study had good compliance with the medication regimen.

DISCUSSION

LUTS encompasses a variety of symptoms that can be divided into three groups, including voiding symptoms (weak stream, intermittency, and straining to void), storage symptoms (frequency, urgency, and nocturia), and postvoid symptoms (incomplete bladder emptying, and terminal dribbling) [1]. Therefore, various pharmacological options are available for different groups of symptoms. The primary treatment option for symptoms relating to BPH is α-blockers, which can be used in combination with 5-α-reductase inhibitors in men with enlarged prostate gland (>40 mL) [15]. However, these drugs are usually effective in treating only voiding symptoms and they have a limited role with respect to storage symptoms [3,4,16]. Thus, the current European Association of Urology guidelines recommend that when symptom relief is insufficient with α-blocker alone, they can be used in combination with anticholinergics [15]. Singh et al. [5] reported that IPSS in patients receiving α-blocker plus anticholinergics was significantly reduced by 7.90 versus a 6.27 decrease in α-blocker monotherapy group and asserted that this may be associated with increased bladder capacity due to anticholinergic treatment. Only 30% of BPH patients with OAB symptoms have been shown to improve with α-blocker monotherapy, whereas 75% of patients undergoing treatment with an additional anticholinergic agent were found to show improvement of OAB symptoms [7].

Despite the high prevalence of OAB symptoms in men with BPH, these symptoms are commonly under- or inappropriately treated with anticholinergics in daily practice [2]. The reasons for this are probably because, firstly, it is difficult to clinically distinguish between symptoms related to OAB and BPH, and secondly, there is a perceived risk of developing AUR [2]. Therefore, in this study we investigated the efficacy and safety of a standard dose of an anticholinergic in patients who had previously received low doses of anticholinergics and showed poor efficacy. Numerous previous studies have demonstrated the efficacy and safety of several doses of anticholinergics in treating men with OAB symptoms related to BPH. However, to the best of our knowledge, this study is the first to demonstrate the effectiveness and safety of an anticholinergic, when the dose was increased in the same patients who had previously received a low dose.

Particularly in our study, nocturia has been importantly considered as an inclusion criterion for 'poor efficacy' by adding '≥2 points' in the OABSS Q2, because nocturia has been known as the most bothersome symptom among the voiding symptoms and refractory to medical therapy [17]. The most important and meaningful result of this study is that IPSS questions relating to storage symptoms (Q2, 4, and 7) showed a stronger tendency toward improvement than those relating to voiding symptoms (Q1, 3, 5, and 6). Decreases in all four voiding symptom subscores at V1 (4 weeks after initiation of treatment with a standard dose anticholinergic) were not statistically significant, whereas the subscores of the storage symptoms showed significant decreases. Moreover, most OABSS questions at either at V1, or V2 (12 weeks after initiation of treatment with a standard dose anticholinergic) showed significant improvements (Table 2). Our findings are similar to the results reported by the NEPTUNE study group, where combination of solifenacin (6 mg) plus tamsulosin was only noninferior to tamsulosin monotherapy in reducing the mean total IPSS, whereas combination therapy resulted in significant improvement in the IPSS storage subscore compared with tamsulosin monotherapy [6]. Based on these findings, it can be assumed that anticholinergic therapy may specifically improve storage symptoms by increasing functional bladder capacity.

It is certainly the case that not all patients with BPH would benefit from anticholinergic therapy. In the SATURN study, solifenacin therapy did not result in significant additional benefits to the total IPSS in the overall study population, it showed significant improvements in the total IPSS, along with the IPSS storage subscore, micturition frequency, and urgency episodes in patients with two or more urgency episodes per 24 hours and eight or more micturitions per 24 hours [18]. Therefore, in this study, we only included patients showing poor efficacy in OAB symptoms improvement on the basis of OABSS, regardless of prostate pathology or prostate size, to highlight storage symptoms. Indeed, there were significant improvements in the total IPSS, along with the storage subscore and OABSS, in our patient cohort. The results here may provide a useful guide on when to use anticholinergics in patients with BPH based on OABSS questionnaires. On the contrary, our results do not show that OAB symptoms are fully recovered by dose escalation alone. But rather, it shows only that the standard dose anticholinergic treatment can improve symptoms when compared to those with initial low dose treatment.

In our study, we primarily investigated the effect of

https://doi.org/10.4111/icu.20200053

increasing dose from low-dose to standard dose anticholinergics (solifenacin 5 mg) in the same patient. It would be interesting to raise the dose of solifenacin to 10 mg and observe the efficacy and safety of the medication. Lee et al. [19] previously reported an increase of 17% and 4% in the incidence of dry mouth and AUR respectively, when the dose of solifenacin was raised from 5 mg to 10 mg. Conversely, the SATURN study also reported that patients receiving all three solifenacin doses (3, 6, and 9 mg) showed good tolerance with respect to adverse effects, as there were no significant increases in PVR or the rate of AUR necessitating catheterization [18]. However, the NEPTUNE study revealed that no additional benefits were seen in patients receiving 9 mg solifenacin compared with those receiving 6 mg, regarding frequency, urgency, and total IPSS [6]. These findings may be due to a possible plateau of the efficacy and tolerable adverse effects of solifenacin at 6 mg. It can be explained by the fact that anticholinergic agent inhibits muscarinic receptors in the bladder that may result in decreased detrusor pressure owing to decreased bladder contractions [5]. In our patient cohort, although an increase in PVR was seen from V0 to V2 (36.40 to 68.90, p=0.015), the amount of increase might not be considered to be serious enough to cease the dose escalation. In addition, no patient experienced AUR following administration of 5 mg solifenacin, with only a small minority experiencing minor adverse effects including thirst and constipation. Based on our results and previous data, it can be assumed that standard dose (5 mg) solifenacin may effectively improve OAB symptoms without the risk of AUR, and there may be no need to further increase the dose as this may not provide additional benefits. However, as dose escalation of anticholinergic drug may possibly increase the amount of PVR as seen in our results, the PVR should be monitored with caution during the follow-up.

The major limitation of this study is first, its retrospective design, and therefore, risk of selection bias may exist. Second is that the study design cannot exclude the possibility of symptom improvement due to the use of different kinds of anticholinergics. Because this study is not a prospective randomized clinical trial, but rather a retrospective, observational study based on the real practice data, it was difficult to collect data from patients who received the same agent with increased dose after unsatisfactory improvement with lose dose anticholinergic treatment. Because solifenacin 5 mg is widely prescribed in Korea, we investigated the effect of solifenacin 5 mg in patients with unsuccessful results after lose dose treatment for convenience. Third, it is also a limitation that the prostate volume was not included in the analysis. Lastly, there might be risk of bias related to different duration of low-dose anticholinergic treatment, although almost half of the patients (272 patients) were within 1 to 11 months of low-dose treatment. A large scale, randomized, double-blind phase 2 study is mandated to adjust certain flaws of the study design to confirm our data. However, our preliminary data have their own importance in a unique design that demonstrates the effect of increasing an anticholinergic drug dose in patients with OAB symptoms while taking a low-dose of an anticholinergic agent.

CONCLUSIONS

This large retrospective study confirmed that the use of standard doses of anticholinergic drugs could improve especially the storage symptoms without increasing the likelihood of adverse events in male patients with LUTS who showed poor efficacy following low-dose anticholinergic treatments. However, post void urine should be monitored during the follow-up.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ACKNOWLEDGMENTS

This study was supported by Astellas Pharm Korea, Co.

AUTHORS' CONTRIBUTIONS

Research conception and design: Myungsun Shim and Cheol Young Oh. Data acquisition: Myungsun Shim, Jong Keun Kim, Woo Jin Bang, Yong Seong Lee, Sung Tae Cho, Jin Seon Cho, Kwan Joong Joo, Jae Seog Hyun, Byung Hoon Kim, Jong Bok Lee, Young Jin Seo, and Cheol Young Oh. Statistical analysis: Myungsun Shim. Drafting the manuscript: Myungsun Shim. Critical revision of the manuscript: Myungsun Shim and Cheol Young Oh. Obtaining funding: Cheol Young Oh. Administrative, technical, or material support: Myungsun Shim and Cheol Young Oh. Statistical analysis: Myungsun Shim. Supervision: Jin Seon Cho and Cheol Young Oh.

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