Short-term effects of oxybutynin dosage in individuals with neurogenic bladder following spinal cord injury: A retrospective cohort study

SIRINTIP BOONJARASPINYO[1,2], JITTIMA SAENGSUWAN[3], PATPIYA SIRASAPORN[3] and BANDIT THINKHAMROP[4]

[1]Department of Community, Family and Occupational Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; [2]Epidemiology and Biostatistics Program, Faculty of Public Health, Khon Kaen University, Khon Kaen 40002, Thailand; [3]Department of Rehabilitation Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; [4]Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Khon Kaen 40002, Thailand

Received April 11, 2024; Accepted June 28, 2024

DOI: 10.3892/br.2024.1823

Abstract. The aim of the present study was to determine the relationship between dose of oxybutynin and reduction in detrusor pressure in individuals with neurogenic bladder (NGB) secondary to spinal cord injury (SCI). The hospital-based data were examined for all individuals with NGB and SCI who were admitted for urological evaluation between January 1999 and December 2016. Patient characteristics, urodynamics and bladder management details were collected at pre-treatment and post-treatment. The primary outcome used to assess oxybutynin treatment was the change in detrusor pressure (P_{det}). Analysis of covariance (ANCOVA) was used to investigate the relationship between dosage of oxybutynin and decrease in P_{det}. A total of 245 participants (112 who received no medication and 133 treated with oxybutynin) were included. After controlling for confounding factors, each 1 mg increase in oxybutynin was associated with a mean decrease of 0.9 cmH_2O in P_{det} (95% CI, -1.4 to -0.3). Stratifying bladder management by indwelling catheter, oxybutynin at a dose of 1 mg was associated with a mean decrease in P_{det} of 0.5 cmH_2O (95% CI, -1.4 to 0.4) in patients with indwelling catheters and 1.0 cmH_2O (95% CI, -1.7 to -0.3) in patients with clean intermittent catheterization and balanced bladder. This study provided guidance for setting the starting dose of drugs associated with response variability in NGB with SCI. Oxybutynin is deemed to be clinically effective for managing NGB in patients with SCI.

Correspondence to: Dr Jittima Saengsuwan, Department of Rehabilitation Medicine, Faculty of Medicine, Khon Kaen University, 123 Mittraphap Road, Muang, Khon Kaen 40002, Thailand
E-mail: sjittima@kku.ac.th

Key words: neurogenic bladder, oxybutynin, spinal cord injury, indwelling catheter, short-term

Introduction

Neurogenic bladder (NGB) is a disorder of the lower urinary tract that can lead to problematic symptoms and complications including urinary incontinence, increased urinary frequency and urgency, risk for infection and upper urinary tract deterioration (1). Globally, the reported prevalence of spinal cord injury (SCI) ranges from 236 to 1,009 per 1,000,000 individuals in 2011 (2), while in Thailand, the incidence ranges from 5.8 to 23.0 per 1,000,000 (3). The incidence of neurogenic bladder dysfunction varies depending on the primary cause. Although, to the best of our knowledge, no epidemiological studies on neurogenic bladder with SCI have been conducted in Thailand, it is estimated that 70 to 84% of patients with SCI will develop bladder dysfunction (4,5). The symptoms of NGB vary and can range from an underactive bladder with urinary retention or difficulties emptying the bladder to an overactive bladder with urgency and urge incontinence, depending on the level of SCI. These symptoms, especially those caused by neurogenic detrusor overactivity (NDO) and detrusor external sphincter dyssynergia, can lead to severe complications such as upper urinary tract dilatation, urinary tract infection or renal failure (6).

One of the goals of NGB management is to prevent high detrusor pressure (P_{det}), which can lead to upper urinary tract deterioration (4). Antimuscarinic drugs, a subtype of anticholinergic drugs, are the main pharmacological treatment for NDO (7,8). Multiple choices of antimuscarinic drugs are available, such as oxybutynin, trospium, tolterodine, darifenacin and solifenacin, each with its own advantages and disadvantages (7,8). The present study focused on oxybutynin, which is widely used in Thailand. Oxybutynin is primarily indicated for the treatment of NDO and is the most widely prescribed compound for NDO worldwide (9,10). Oxybutynin is a tertiary amine with both antimuscarinic and direct muscle relaxant effects. The typical starting dose for adults is one 5 mg tablet two to three times per day for immediate release, and the maximum daily dose should not exceed four 5 mg tablets (up to 45 mg daily for immediate release as tolerated) (7,11).

Several studies have shown that oral oxybutynin is effective in controlling symptoms of overactive bladder (12-14). However, dry mouth is a common side effect in the oxybutynin group compared with other treatments (13-15). In Thailand, oxybutynin is the most commonly used first-line drug in clinical practice due to its cost-effectiveness, (16) but published clinical evidence on effectiveness is scarce. With guidance for optimal dosage, cystometric parameters can be better controlled and the incidence of adverse effects may be reduced.

While there exists a substantial body of evidence regarding the efficacy of oxybutynin in treating NGB among individuals with SCI (12-14), no study to date has established the dose-response relationship of oxybutynin. The present study aimed to determine the dose response relationship of oxybutynin for reducing P_{det} in patients with NGB and SCI under real-world clinical care conditions. The results of this study reflect 'real-life' clinical practice and may provide guidance for the clinical use of antimuscarinic medications.

Materials and methods

Study design and participants. The study was conducted as a retrospective cohort study using hospital-based data at Srinagarind Hospital, Khon Kaen University (Khon Kaen, Thailand), where the data was collected between January 1999 and December 2016. This study was approved by the Center for Ethics in Human Research, Khon Kaen University, Thailand (approval no. HE651472).

The medical records of neurogenic bladder due to spinal cord injury were chronologically selected to meet the following inclusion criteria: i) Patients aged >18 years; ii) first treatment within 5 years after SCI; iii) duration time after first treatment from ~1 month to 2 years; iv) either no medication treatment, or antimuscarinic treatment with oral oxybutynin IR in variable doses; and v) a urodynamic assessment both of baseline and first follow up. Patients were excluded based on them receiving multiple NGB medications at the same time of study. The study flowchart is depicted in Fig. 1.

Outcomes. The primary outcome was individual P_{det} reduction after various doses of oxybutynin treatment. The secondary outcome was the change in cystometric capacity after oxybutynin treatment. P_{det} reduction was calculated from the difference between the highest detrusor pressure measured during filling cystometry at baseline and follow up. Change in cystometric capacity was calculated from the difference between bladder volume at the end of the filling cystometrogram at baseline and follow up. Urodynamic testing was performed using a standardized procedure as described previously (17). The study terminology and the urodynamic parameters followed the International Continence Society guidelines (18).

Statistical analysis. The sample size was calculated based on the proposed clinically meaningful P_{det} reduction of 10 cmH_2O. A standard deviation of 25 with a power of 80% (two-sided test; α=0.05) was assumed. Based on the sample size calculation using methods proposed by Borm *et al* (19), a sample size of 103 has a power of 80% to detect a mean difference of at least 10 cmH_2O.

Table I. Demographic characteristics of samples between treatment groups.

Parameter	Oxybutynin	No medication
N patients	133	112
Age at diagnosis, years	43.5 (14.8)	48.1 (15.5)
Sex, female/male	34.6/65.4	25.0/75.0
Suprasacral injury	88.0	77.7
Completeness of lesion	35.3	19.6
Vesicoureteral reflux	18.6	5.0
Duration after SCI, years	1.3 (1.3)	0.8 (1.2)
Duration after first treatment, years	1.0 (0.4)	1.0 (0.3)
Bladder management		
CIC and balanced bladder	54.1	81.2
Indwelling urinary catheter	45.9	18.8
Baseline values		
Maximum detrusor pressure, cmH_2O	52.3 (26.1)	31.2 (19.0)
Cystometric capacity, ml	264.2 (132.1)	336.6 (156.5)

Data are presented as mean (standard deviation) or % variable.

STATA (STATA 18.0 for Windows; StataCorp LP) was used to perform Analysis of Covariance (ANCOVA) to demonstrate changes in P_{det} or cystometric capacity between the control group (no medication) and the experiment group (oxybutynin in various doses). The results are reported as mean ± standard deviation of pre- and post-treatment, mean difference, 95% confidence interval (CI) and P-value, based on ANCOVA, adjusted for baseline P_{det} or cystometric capacity value, age (years), sex, level of SCI, completeness of lesion, vesicoureteral reflux (VUR) and bladder management. Additionally, analysis was stratified by bladder management to explore whether bladder management affects the bladder response to the reduction in P_{det} (ANCOVA). The dose-response relationship between oxybutynin dosage and reduction in P_{det} was established by plotting a fitted line of the mean P_{det} difference using ANCOVA, with a confidence interval. For all analyses, significance was set as α=0.05 and two-sided testing was performed. P<0.05 was considered to indicate a statistically significant difference.

Results

The medical records of 245 eligible patients with NGB due to SCI were enrolled to the present study. Among the study patients, 133 were taking oxybutynin, while 112 were not taking any medication. The age at diagnosis in the oxybutynin group was 43.5±14.8 years vs. 48.1±15.5 years in the no-medication group. The proportion of women in the oxybutynin group was higher compared with that in the no medication group (34.6 vs. 25.0%). At baseline, there was a higher prevalence of VUR in the oxybutynin group compared with the no-medication group

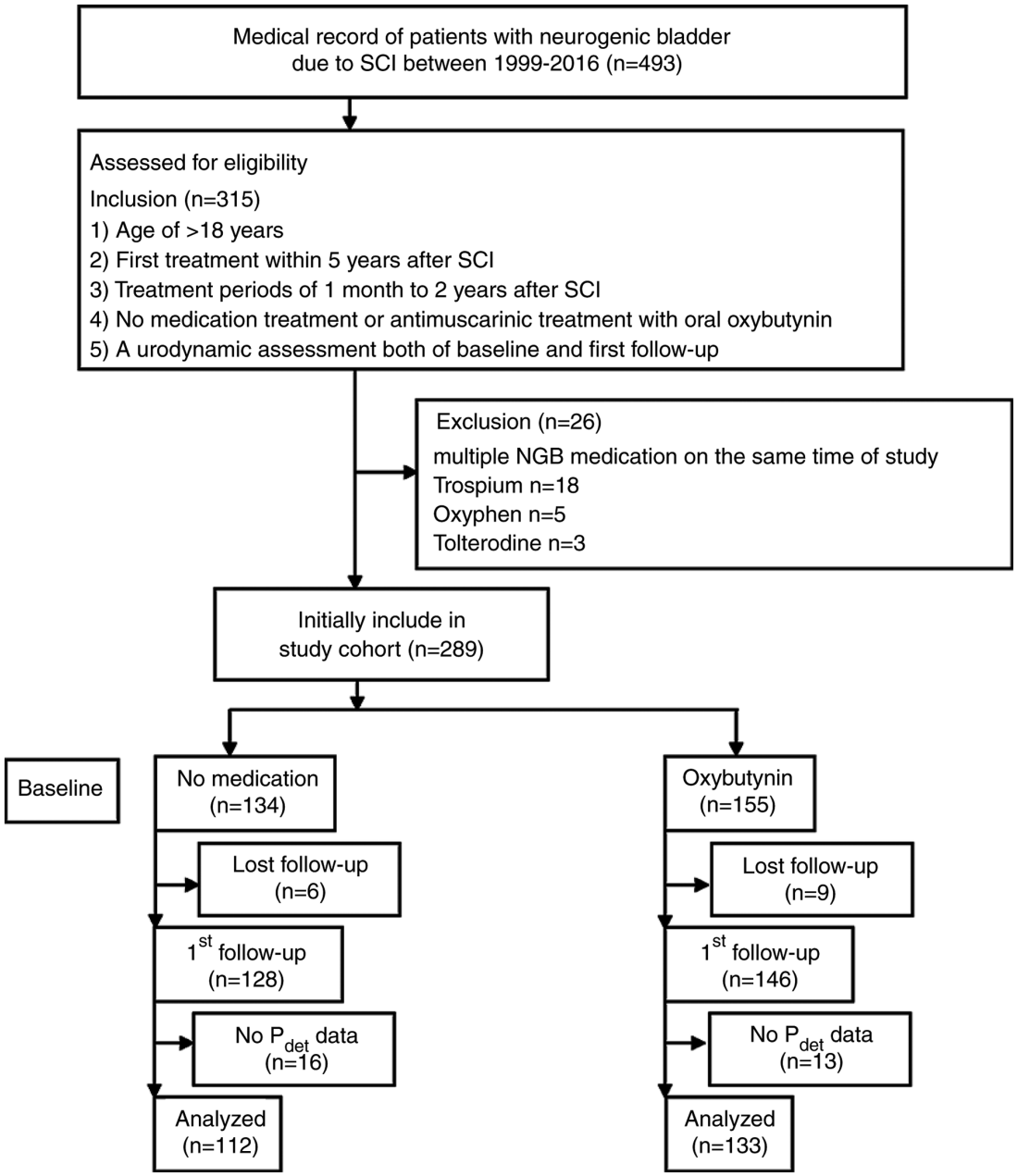

Figure 1. Flow diagram of the study cohort. SCI, spinal cord injury; NGB, neurogenic bladder; P_{det}, detrusor pressure.

(18.6 vs. 5.0%). There was a higher proportion of participants with indwelling catheter management in the oxybutynin group (45.9 vs. 18.8%). The distribution of level of injury, completeness of lesion, duration after SCI, duration after first treatment and baseline values of urodynamic variables are provided in Table I.

The primary outcome, the dose-response relationship of oxybutynin for the mean of P_{det} reduction, was well described by ANCOVA, and was adjusted for baseline and age (years), sex, level of injury, completeness of lesion, VUR and bladder management. The decrease in P_{det} by 1 mg of oxybutynin was ~0.9 cmH_2O (95% CI, -1.4 to -0.3; P=0.002). Fig. 2 shows the fit of the dose-response relationship for the reduction in P_{det} and oxybutynin monotherapy. The secondary outcome showed that with every 1 mg oxybutynin increase, the cystometric capacity increased by ~1.3 ml (95% CI, -1.5 to 4.0; P=0.358).

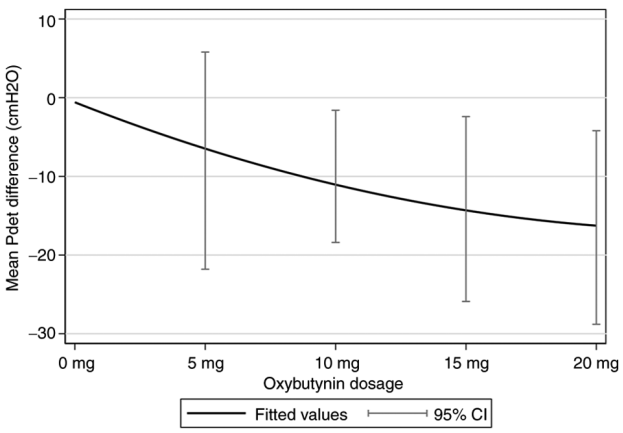

Figure 2. Dose-response relationship between mean P_{det} difference and oxybutynin monotherapy.

Table II. Mean differences of detrusor pressure and cystometric capacity, adjusted for their baselines at various doses of oxybutynin after first time treatment.

Variable	n	Pre-treatment mean (SD)	Post-treatment mean (SD)	Mean difference	95% CI	P-value
Detrusor pressure						
0 mg Oxybutynin	112	31.2 (19.0)	41.4 (27.4)	Reference		
5 mg Oxybutynin	15	36.7 (17.3)	36.2 (22.2)	-8.0	-21.8 to 5.8	0.255
10 mg Oxybutynin	63	46.3 (21.8)	38.1 (20.2)	-10.0	-18.4 to -1.6	0.019
15 mg Oxybutynin	29	63.8 (25.7)	42.3 (28.5)	-14.2	-25.9 to -2.4	0.018
20 mg Oxybutynin	26	63.0 (31.8)	43.4 (27.6)	-16.5	-28.8 to -4.2	0.009
Every 1 mg oxybutynin increase		-	-	-0.9	-1.4 to -0.3	0.002
Every 5 mg oxybutynin increase		-	-	-4.4	-7.1 to -1.6	0.002
Cystometric capacity						
0 mg Oxybutynin	112	336.6 (156.5)	305.5 (148.9)	Reference		
5 mg Oxybutynin	15	242.4 (158.1)	229.1 (132.8)	-36.6	-115.1 to 41.8	0.358
10 mg Oxybutynin	63	261.2 (129.8)	282.3 (143.4)	8.6	-37.0 to 54.1	0.711
15 mg Oxybutynin	29	274.4 (134.9)	319.5 (139.1)	51.1	-10.1 to 112.3	0.101
20 mg Oxybutynin	26	272.8 (124.7)	236.8 (134.5)	1.4	-62.3 to 65.0	0.966
Every 1 mg oxybutynin increase				1.3	-1.5 to 4.0	0.358
Every 5 mg oxybutynin increase				6.4	-7.3 to 20.1	0.358

Mean difference and 95% CI were based on ANCOVA, adjusted for baseline and age (years), sex, level of SCI, completeness of lesion, VUR and bladder management. SD, standard deviation.

The urodynamic values at pre- and post-treatment at various oxybutynin doses are presented in Table II.

The stratified analysis showed the effects of oxybutynin in patients with either indwelling catheter or clean intermittent catheterization (CIC) and balanced bladder were different (Table III). The group of indwelling catheter management showed that mean P_{det} was reduced during treatment of oxybutynin by 0.5 cmH_2O (95% CI, -1.4 to 0.4; P=0.270), and CIC and balanced bladder by 1.0 cmH_2O (95% CI, -1.7 to -0.3; P=0.006). The mean cystometric capacity increased by 2.9 ml (95% CI, -2.0 to 7.7; P=0.243) in indwelling catheter with oxybutynin treatment, while it increased by 0.03 ml (95% CI, -3.4 to 3.5; P=0.985) in patients without indwelling catheter management.

Discussion

This retrospective cohort study aimed to investigate the dose-response relationship of oxybutynin for reducing detrusor pressure in individuals with NGB following SCI under real-world clinical care conditions. The present study effectively demonstrated a dose response for oxybutynin: With every 1 mg increase in dose, P_{det} was decreased by 0.9 cmH_2O.

Although an indwelling urethral catheter increases the risk of UTI, renal impairment, bladder stone formation, urethral stricture, urethral erosion and bladder cancer, some patients require this bladder management method due to personal restrictions such as impaired hand function for self-intermittent catheterization or limited assistance from a caregiver (20-22). The present study further stratified patients based on bladder management methods to explore whether bladder management method affected the response in P_{det} and bladder capacity. The study found that P_{det} in patients with indwelling catheters responded less to oxybutynin compared with patients without indwelling catheters (-0.5 cmH_2O vs. -1.0 cmH_2O for every 1 mg increase in oxybutynin), although they regained more bladder capacity (2.9 ml). The current study showed the same trend as the previous study of Kim *et al* (23), where patients who require chronic indwelling catheters for bladder management who take oxybutynin regularly have improved bladder compliance and lower bladder leak point pressures.

The usual starting dose of oxybutynin for adults with NGB is 5 mg (11). The present study categorized oxybutynin into four groups based on the available doses in the market. During this study, patients received doses ranging from 5 to 20 mg/day. Common adverse effects of oxybutynin are dry mouth, constipation, headache, dyspepsia and dry eyes (24). In particular, dose-dependent dry mouth is most commonly reported (25). Several trials and meta-analyses have shown that oxybutynin has a clinically superior efficacy profile (26-28), but it is limited by low tolerance due to side effects, which leads to higher withdrawals rates compared with other antimuscarinic medications, such as tolteridine (27). In fact, patients receiving low-dose oxybutynin should have fewer adverse effects leading to improved compliance with an antimuscarinic treatment than those receiving the high dose. Based on our findings, physicians could adjust the optimal dosage of oxybutynin for individual patients based on their detrusor pressure and bladder management methods. This will result in a more precise dosage of anticholinergic treatment for each patient. For example, if a clinically meaningful reduction of P_{det} of 10 cmH_2O is desired in patients with CIC and balanced bladder, a recommended oxybutynin dosage would

Table III. Mean differences of detrusor pressure and cystometric capacity, adjusted for their baselines at various doses of oxybutynin after first time treatment stratified by catheter management method.

Variable	Mean difference	95% CI	P-value
Indwelling catheter (n=75)			
Detrusor pressure			
Every 1 mg oxybutynin increase	-0.5	-1.4 to 0.4	0.270
Every 5 mg oxybutynin increase	-2.5	-7.1 to 2.0	0.270
Cystometric capacity			
Every 1 mg oxybutynin increase	2.9	-2.0 to 7.7	0.243
Every 5 mg oxybutynin increase	14.3	-10.0 to 38.7	0.243
CIC & balanced bladder (n=143)			
Detrusor pressure			
Every 1 mg oxybutynin increase	-1.0	-1.7 to -0.3	0.006
Every 5 mg oxybutynin increase	-5.0	-8.5 to -1.5	0.006
Cystometric capacity			
Every 1 mg oxybutynin increase	0.03	-3.4 to 3.5	0.985
Every 5 mg oxybutynin increase	0.2	-17.1 to 17.4	0.985

Mean difference and 95% CI were based on ANCOVA, adjusted for baseline and age (years), sex, level of SCI, completeness of lesion and VUR.

be 10 mg. However, if a larger decrease in P_{det} is desired, then increasing the dosage, combining with other anticholinergic drugs or changing the method of administration, should be implemented (29,30).

The current retrospective study at a supertertiary hospital may inherently introduce selection bias. The included population likely represents a more complex patient profile compared with a general hospital setting. Additionally, inherent limitations in retrospective data, including potentially incomplete records and patients lost to follow-up, may further compromise generalizability. There were no data regarding the compliance for medications and medical adverse effects of each participant. Apart from an improvement in urodynamic data, which may imply reduced risk of upper urinary tract deterioration in the future, one of the aims of anticholinergic treatment is to achieve continence to allow better quality of life in patients without indwelling catheterization (29,31). However, the present study could not consider on this aspect due to incomplete medical records. Hospital-based data from single institutions may not be generalizable to other settings with different patient demographics, practices, healthcare infrastructure and resources. This study's setting in a supertertiary center, which handles more complex cases, may skew results if the patient population is not representative of the broader community. The change of cystometric capacity in relation to oxybutynin dosage should be interpreted with caution due to the non-linear nature of the relationship. The duration after SCI may affect the response to antimuscarinic medication: Since patients began their first antimuscarinic medication at ~1.3 years after their SCI, they may have a lower response to medication compared to groups with earlier treatment (31).

In conclusion, the findings of the present study offer insights for determining the initial dosage of medications with variable responses in individuals with neurogenic bladder due to SCI. We found that increasing the dose by 5 mg resulted in a decrease of P_{det} by 4.4 cmH_2O.

Acknowledgements

Not applicable.

Funding statement

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

All authors were responsible for the research conceptualization, study design, and manuscript drafting. SB, JS, PS and BT were involved in data collection, analysis, and interpretation. SB and JS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics of approval statement and patient consent statement

Ethical approval for this study was obtained from the Khon Kaen University Ethics Committee in Human Research (approval no. HE651472). The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/Institutional Review Board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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