ORIGINAL ARTICLE

Combined low dose local anesthetics and opioids versus single use of LA for transurethral urological surgery: A meta-analysis

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Abstract

Introduction: The combination of reduced dose of local anesthetics (LA) and highly lipid-soluble synthetic opioids for patients undergoing transurethral surgery could reduce block duration and side-effects. However, it remains unclear what are the most appropriate levels of low dose and the extent to which the side-effects could be controlled. A meta-analysis was conducted to address this concern.

Materials and Methods: Based on twelve randomized controlled trials, this meta-analysis pooled previous results to generate integrated evidence.

Results: Combined low dose of LA and opioids had similar sensory block and significantly shorter motor block duration (weighted mean difference: –39.31 min, 95% confidence interval (CI): –50.58–−28.05, $P < 0.00001$) compared with single use of LA. There was no evidence of higher risk of analgesic failure in the combination group. In addition, combined low dose LA and opioids was associated with significantly reduced rate of postoperative hypotension (risk ratios (RR): 0.60, 95% CI: 0.37–0.96, $P = 0.03$) and shivering (RR: 0.27, 95% CI: 0.11–0.64, $P = 0.003$), but with higher rate of sedation (RR: 3.14, 95% CI: 1.02–9.66, $P = 0.05$).

Conclusion: Combined low dose LA and opioids is a better choice for patients received transurethral surgery compared with single use of intrathecal LA.

Key words: Intrathecal anesthesia, local anesthetics, opioids, transurethral surgery

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Introduction

Local anesthetics (LA) based intrathecal anesthesia has been widely used for transurethral surgery since it allows early recognition of symptoms caused by bladder perforation, over-hydration and transurethral resection of prostate (TURP) syndrome.[1] A large proportion of the patients undergoing urological surgery, such as TURP and (transurethral resection of bladder tumor (TURBT) are elderly people who have coexisting cardiac, pulmonary or other comorbid disease.[2] Although LA based intrathecal anesthesia has advantages in lower postoperative pain score, less demand for analgesics during recovery and shorter recovery time compared with general anesthesia.[3,4] It is also associated with prolonged motor block and several side effects, such as disturbed proprioception, hypotension and urinary retention that are dose dependent.[5] These limitations may increase management complexity of the comorbid diseases, interfere with early mobilization and prolong hospital stay of the patients. Therefore, reducing the side effects associated with intrathecal anesthesia is quite helpful to support better postoperative management.

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Low dose LA could reduce the side-effects. However, this might increase the risk of short analgesia or even block failure, which may require general anesthesia as a remedy. Opioids are potential adjuvants for intrathecal anesthesia based on LA. A series of randomized controlled studies were conducted to evaluate the combination of the highly lipid-soluble synthetic opioids and reduced concentration of local anesthetic agents for patients undergoing transurethral surgery and found the combination could effectively reduce block duration and side-effects.[6-8] Therefore, one possible solution is to decrease the dose of LA to minimal effective level in combination with an opioid.

However, it remains unclear what are the most appropriate level of dose decrease and the extent to which the side-effects could be controlled. This meta-analysis is aimed at pooling the results of previous randomized controlled trials (RCTs) to generate integrated evidence for better understanding of the combination of intrathecal LA and adjuvant opioids for patients undergoing transurethral surgery.

Materials and Methods

Databases and search strategy

This study was conducted according to the PRISMA statement recommended by the Cochrane Collaboration.[9] Databases including MEDLINE, EMBASE and Clinical Trails.com were search from January 1990 to May 2014. The following search terms and strategy be applied: ("spinal" OR "intrathecal") AND ("analgesia" OR "anesthesia" OR "anesthesia") AND ("opioid" OR "fentanyl" OR "sufentanil" OR "morphine") AND ("urological" or "transurethral"). Reference list of eligible studies was manually searched to identify additional qualified studies. No language restriction was set when searching for eligible studies.

Selection criteria

Two authors (YD and ML) independently performed the search process. Studies have to meet the following criteria for inclusion: (1) Randomized controlled studies (RCTs); (2) studies compared the combination of adjuvant opioids and reduced dose of intrathecal LA and single use of intrathecal LA in transurethral surgery; (3) data of anesthesia efficiency and side effect data could be extracted. Queries ineligibility of the studies were resolved through group discussion.

Data extraction

Two authors (YD and ML) independently extracted data from original studies. Another author (YC) was responsible for cross-checking. Discrepancies were resolved through discussion with two additional authors (LC and QZ). Basic study characteristics, including a year of publication, number of patients recruited, type of surgery, regimens of LA and opioids were extracted. To evaluate the efficiency and side-effects, the continuous data, including motor block and sensory block duration and dichotomous data, including need for additional anesthesia, postoperative hypotension, nausea, vomiting, bradycardia, shivering and sedation was extracted for meta-analysis.

Quality assessment

Quality of the studies included was assessed with a modified 4-item, 7-point Oxford scale assessing the method of randomization, concealment of treatment allocation, degree of blinding, and reporting of dropouts.[10]

Data analysis

RevMan version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for data analysis. For continuous data, weighted mean difference (WMD) with 95% confidence interval (CI) was calculated. For dichotomous data, risk ratios (RR) with 95% CI were calculated. Heterogeneity between studies was assessed by Chi-square-based Q-test and I^2. $P < 0.05$ of the Q test $I^2 > 50\%$ indicates significant heterogeneity. Data analysis was primary performed based on fixed-effects model. If the results confirmed no significant heterogeneity, fixed-effects model based on Mantel–Haenszel method was applied. However if the result indicated significant heterogeneity, the source of heterogeneity was then further analyzed. If the heterogeneity were not caused by clinical or methodological differences among trails, random effects model would be used.

Results

Selection of trials

Through searching in databases and screening with preset criteria, a total of twelve studies[6-8,11-19] were included for following a meta-analysis. The search process was described in Figure 1.

Basic characteristics of studies included

The basic characteristics of the twelve trials and quality their quality score were summarized in Table 1. A total of 373 and 253 patients were included in experiment and control group, respectively. The trial size ranged from 30 to 90 patients. Eight studies used the bupivacaine as LA, of which 5 tested the combination of reduced dose with fentanyl 1 tested the combination of reduced dose with sufentanil and 2 tested the combination with sufentanil or fentanyl. Two studies evaluated the combination between levobupivacaine and fentanyl or sufentanil, 1 assessed tetracaine with fentanyl and one assessed ropivacaine with fentanyl. The LA decrease ranged from 10% to 60%, and the median decrease was 33%. The quality score of the trails ranged from 2 to 5, and the median quality score was 3.5. Only one study had quality score lower than 3

and was considered as low-quality trial. All studies had a randomized and double-blind design. Eight studies have adequately described randomization, seven studies reported concealment of treatment allocation. However, no study had a follow-up of the patients. Since Gupta *et al*.'s[15] and Akan *et al*.'s[17] study compared the combination of reduced LA and fentanyl or sufentanil, respectively, "(F)" (fentanyl) and "(S)" (sufentanil) are used to label the combination of these two studies in forest figures.

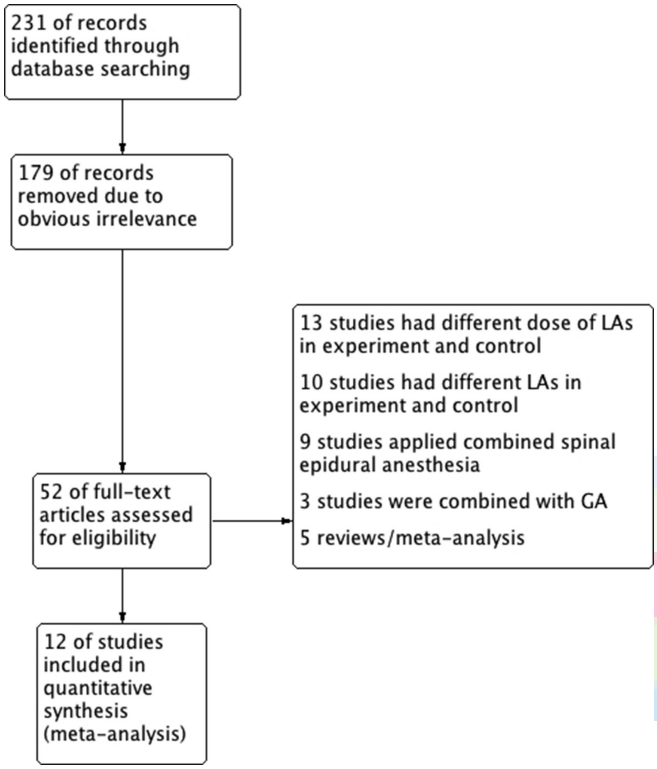

Figure 1: The search process

Efficiency of combined lower dose local anesthetics and opioids versus single use of LA

Duration of sensory block and motor block was used to assess the efficiency of combined lower dose LA and opioids (experiment) versus single use of LA (control).

Duration of sensory block

Seven studies reported duration of sensory block. Among them, one study reported time to L4 regression.[18] two studies reported regression time to S_1;[8,12] one study reported regression time to S_2.[7] four studies reported time to the two-segment regression,[7,8,12,17] one studies reported regression time to T12,[15] one study did not give a definition of regression.[14] In general, the duration of sensory block of combined lower dose LA and opioids was similar to that of single use of LA (WMD: −6.42 min, 95% CI: −16.82–3.99, $P = 0.23$, $I^2 = 94\%$) [Figure 2]. However, due to significant heterogeneity in outcome indicators, subgroup analysis was performed. Subgroup analysis showed that compared with single use of LA, combined lower dose LA had similar regression time to S_1 (WMD: −21.34 min, 95% CI: −48.57–5.88, $P = 0.12$, $I^2 = 8\%$), S_2 (WMD: −4.00 min, 95% CI: −11.75–3.75, $P = 0.31$, I^2 not applicable) and two-segment (WMD: −1.58 min, 95% CI: −5.44–2.28, $P = 0.98$, $I^2 = 0\%$), but with significantly longer duration of regression to T12 (WMD: 20.00 min, 95% CI: 10.20–29.80, $P < 0.0001$, $I^2 = 90\%$) and significantly shorter duration of regression to L4 ($P < 0.00001$) [Figure 2].

Duration of motor block

Nine studies reported duration of motor block,[6-8,12,14-18] which is defined as the time from the end of surgery till full recovery of motor function of the lower extremities. The average duration of motor block in experiment

Table 1: Basic characteristics of trails included

Study	Surgery	Number of patients		LA	LA dose (mg)		LA dose reduction %	Opioid	Opioid dose (mg)	Study quality
		Control	Experiment		Control	Experiment				
Conway *et al.* 1996	TURP or TURBT	14	14	Bupivacaine	15	7.5	50	Meperidine	22	3
Cuvas *et al.* 2010	TURP or TURBT	20	20	Bupivacaine	12.5	11	12	Fentanyl	0.015	4
Kararmaz *et al.* 2003	TURP	20	20	Bupivacaine	7.5	4	47	Fentanyl	0.025	3
Kuusniemi *et al.* 2000	TP	20	40	Bupivacaine	10	7.5/5	25/50	Fentanyl	0.025	4
Walsh *et al.* 2003	TURP	14	14	Bupivacaine	15	10	33	Fentanyl	0.025	3
Zohar *et al.* 2007	TP	25	75	Bupivacaine	7.5	3/4/5	60/47/33	Fentanyl	0.02	2
Gupta *et al.* 2013	TP	30	60	Bupivacaine	7.5	5	33	Sufentanil/ Fentanyl	0.01/0.025	3
Doger *et al.* 2013	TURP	20	20	Bupivacaine	10	7.5	25	Sufentanil	0.005	4
Akan *et al.* 2013	TURP	20	40	Levobupivacaine	10	7.5	25	Sufentanil/ Fentanyl	0.0025/0.025	4
Lee *et al.* 2005	TURP or TURBT	25	25	Levobupivacaine	13	11.5	12	Fentanyl	0.015	5
Chen *et al.* 2001	TURP	15	15	Tetracaine	8	4	50	Fentanyl	0.01	4
Chaudhary *et al.* 2014	TP	30	30	Ropivacaine	2	1.8	10	Fentanyl	0.01	3

TP=Transurethral procedures; TURP=Transurethral resection of prostate; TURBT=Transurethral resection of bladder tumor; LA=Local anesthetics

group was significantly shorter than that of the control groups (WMD: −39.31 min, 95% CI: −50.58–−28.05, $P < 0.00001$, $I^2 = 91\%$) [Figure 3].

Adverse effects of combined lower dose local anesthetics and opioids versus single use of LA

Risk of block failure

Three studies[6,13,18] defined block failure is as demand for supplementary intraoperative systemic opioids. 3/49 in experiment group and 10/49 patients in control group needed supplementary intraoperative systemic opioids [Table 2]. The risk difference was not statistically significant (RR: 0.36, 95% CI: 0.13–1.05, $P = 0.06$, $I^2 = 12\%$) [Table 2].

Four studies[11,13,14,18] defined it as the demand for a general anesthetic. 2/69 in experiment group and 2/69 patients in control group needed general anesthetic. The risk difference was not statistically significant (RR: 1.00, 95% CI: 0.24–4.24, $P = 0.61$, $I^2 = 4\%$) [Table 2].

Postoperative hypotension

Ten studies[6-8,11,12,14,15,17-19] reported data of postoperative hypotension. There were 20/268 and 31/218 cases of postoperative hypotension in experiment and control group, respectively. The rate was significantly lower in experiment than in control group (RR: 0.60, 95% CI: 0.37–0.96, $P = 0.03$, $I^2 = 24\%$) [Table 2].

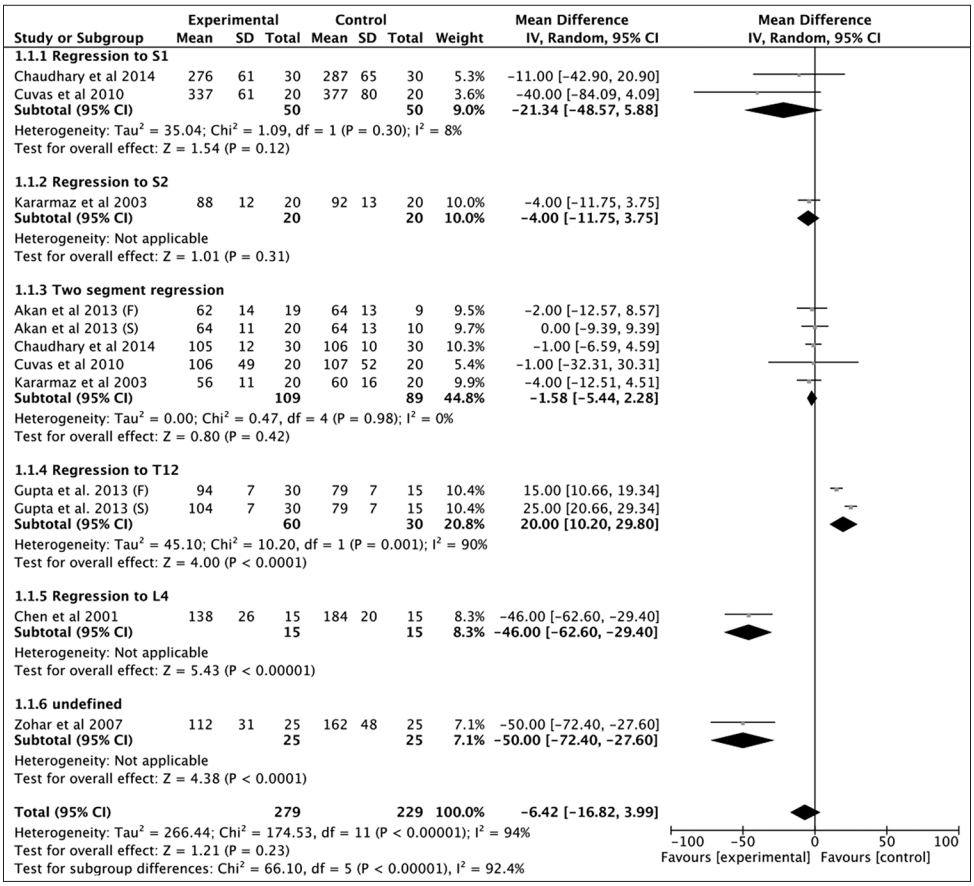

Figure 2: Meta-analysis of duration of sensory block

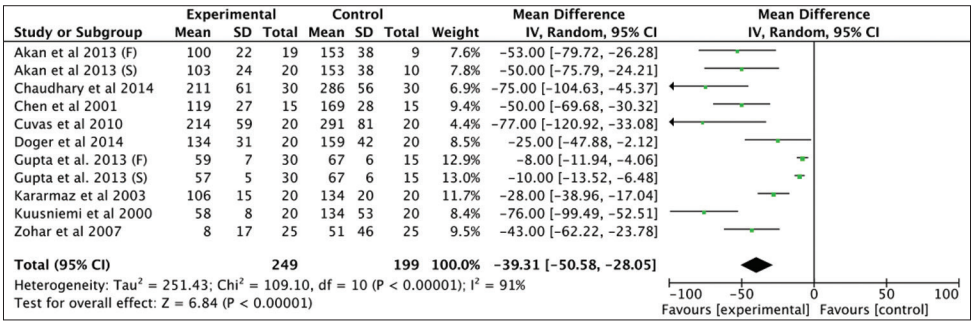

Figure 3: Meta-analysis of duration of motor block

Table 2: A meta-analysis of adverse effects

Adverse effects	Experiment (rate)	Control (rate)	Pooled RR (95% CI)	I2%	P-H	*P*
Supplementary intraoperative opioids	3/49	10/49	0.36 (0.13, 1.05)	12	0.32	0.06
General anesthetic	2/69	2/69	1.00 (0.24, 4.24)	0	0.52	0.61
Hypotension	20/268	31/218	0.60 (0.37, 0.96)	24	0.21	0.03
Nausea	4/263	6/213	0.54 (0.16, 1.78)	0	0.80	0.31
Vomiting	0/120	1/120	0.31 (0.01, 8.28)	-	-	0.49
Bradycardia	12/203	9/153	1.05 (0.50, 2.23)	0	0.57	0.89
Shivering	5/150	20/150	0.27 (0.11, 0.64)	0	0.79	0.003
Sedation	13/149	2/119	3.14 (1.02, 9.66)	0	0.88	0.05

CI=Confidence interval; RR=Risk ratio; P-H=*P* value of Q for heterogeneity test; I^2>50%=High heterogeneity; random effects model was used when P-H>0.1 or I^2>50% Otherwise, fixed-effect model was used

Postoperative nausea

Ten studies[6-8,12,13,15-19] reported results of postoperative nausea, which were 4/263 and 6/213 in experiment and control group, respectively. The rate was similar the two groups (RR: 0.54, 95% CI: 0.16–1.78, $P = 0.31$, $I^2 = 0\%$) [Table 2].

Postoperative vomiting

Six studies[6,7,12,16,18,19] reported results of postoperative vomiting, which were 0/120 and 1/120 in experiment and control group, respectively. The rate was similar the two groups (RR: 0.31, 95% CI: 0.01–8.28, $P = 0.49$, I^2 not applicable) [Table 2].

Postoperative bradycardia

Seven studies[6-8,11,12,15,17] reported results of postoperative bradycardia, which were 12/203 and 9/153 in experiment and control group respectively. The rate was similar the two groups (RR: 1.05, 95% CI: 0.50–2.23, $P = 0.89$, $I^2 = 0\%$) [Table 2].

Postoperative shivering

Eight studies[6-8,11,12,16,18,19] reported results of postoperative shivering, which were 5/150 and 20/150 in experiment and control group respectively. The rate was significantly lower in experiment than in control group (RR: 0.27, 95% CI: 0.11–0.64, $P = 0.003$, $I^2 = 0\%$) [Table 2].

Postoperative sedation

Five studies[8,11,12,15,19] reported results of postoperative sedation, which were 13/149 and 2/119 in experiment and control group, respectively. The rate was significantly higher in experiment than in control group (RR: 3.14, 95% CI: 1.02–9.66, $P = 0.05$, $I^2 = 0\%$) [Table 2].

Discussion

This study observed that combined low dose LA and opioids had similar sensory block efficiency as the use of LA alone. However, the combination contributed to shorter motor block duration. There was no evidence of higher risk of analgesic failure in the combination group, the rate of patients who needed intraoperative analgesia, or a general anesthetic are similar in both experiment and control group. In addition, combined low dose of LA and opioid was associated with significantly reduced rate postoperative hypotension and shivering, but with a higher rate of postoperative sedation.

A large proportion of patients who had TURP or TURBT are elderly patients who frequently had other pulmonary or cardiac diseases.[2] Therefore, reduction of the block level and duration helped to control risks due to cardiopulmonary adverse effects. The type and concentration of the LA used for spinal anesthesia are the two critical determinants of duration and extension of anesthetic block.[1] Lowering the dose of LA can reduce the distribution of the spinal block, but also increase the risk of inadequate sensory block.[7] A series of previous trials showed that use of opioids as adjuvant agents help to enhance analgesia, to ensure the success of anesthesia and to decrease the hemodynamic side-effects.[6,7,19]

Compared with patients who had general anesthetic, patients who had intrathecal anesthesia during surgery did not have significantly reduced stay duration in the recovery room due to the prolonged motor and sensory blocks after the intrathecal administration of an LA.[20] Therefore, shorter motor block is beneficial to support patients in having early mobilization. This study confirmed the motor block duration could be significantly reduced with lowered dose of LA in the experimental group, which is quite supportive to early mobilization after surgery and thus enables better postoperative management. In clinical practice, the main disadvantage of using bupivacaine in day surgery is the long duration of action, recovery and hemodynamic adverse effects like hypotension.[21] Actually, for geriatric patients who had a high incidence of coronary disease, hypotension directly increases the risk of myocardial ischemia.[22] Shivering, a symptom with increased oxygen consumption, is also risky for patients with limited cardiopulmonary reserve.[23] This study confirmed significantly reduced risk of hypotension and shivering in the combination group, suggesting combined lower dose of LA with an opioid is a more suitable choice for geriatric patients who need

transurethral surgery. In addition, intrathecal fentanyl or sufentanil did not significant influence sympathetic response, blood pressure and heart rate in all trials included in this study, suggesting they are safe adjuvants of LA.

Concerning optimal intrathecal drug regimens, bupivacaine and levobupivacaine are the mostly used LA, while fentanyl and sufentanil are the mostly used opioids. Ropivacaine and Tetracaine were also tested for reduced dose in combination with opioids. For bupivacaine, the dose used ranged from 7.5 mg to 12.5 mg and dose reduction ranged from 12% to 60%. For levobupivacaine, the dose used were 10 mg or 13 mg, while the reductions were 7.5% and 11.5% respectively. The dose of fentanyl used ranged from 0.01 to 0.025 mg, while that of sufentanil ranged 0.0025-0.001 mg. For intrathecal fentanyl and sufentanil, the median effective doses (ED50) of are 14 μg and 2.6 μg respectively.[24] Considering the relative potency of intrathecal fentanyl to sufentanil is 1:4.4 at the ED50 level, intrathecal fentanyl 25 μg and sufentanil 5 μg could be considered as an equipotent dose.[24] The original studies did not report the rationale of dose reduction of LA and opioids used in trails. The reason for the dose variability in trails included remained unclear.

This meta-analysis also had several limitations. First, the trials included have a different combination of intrathecal LA and opioids. The LA used includes bupivacaine, levobupivacaine, tetracaine and ropivacaine and opioids used include fentanyl, sufentanil, and meperidine. This is a possible source of clinical heterogeneity. Fortunately, most of the studies evaluated the combination between bupivacaine and fentanyl. In addition, bupivacaine and levo-bupivacaine, fentanyl and sufentanil have similar clinical effects,[25] which ensure the trails could be pooled. Secondly, the number of trials and the number of patients recruited in the trials were relatively small, which increased the possibility of random chance and overestimated the beneficial effects. Thirdly, some of the endpoints measured in original studies had different definitions. This might hamper the reliability of final pooled results. Finally, the rationale for dose reduction was not clearly stated in original studies, which made it impossible to establish a correlation between LA dose reduction and surgery type. These issues are required to be addressed in future study.

Conclusion

Combined low dose LA and opioids is a better choice for patients received endoscopic urological surgery compared with use of intrathecal LA only. The combination supports early mobilization, reduced hospital stay and decreased risk of postoperative hypotension and shivering, two important adverse effects typically for elderly patients.

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