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Mepivacaine Spinal Anesthesia Facilitates Rapid Recovery in Total Knee Arthroplasty Compared to Bupivacaine

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ABSTRACT

Background: Mepivacaine as a spinal anesthetic for rapid recovery in total knee arthroplasty (TKA) has not been assessed. The purpose of this study is to compare spinal mepivacaine vs bupivacaine for postoperative measures in patients undergoing primary TKA.

Methods: Retrospective review of a prospectively collected single-institution database was performed on 156 consecutive patients who underwent primary TKA. Fifty-three patients were administered mepivacaine and 103 patients were administered bupivacaine. Primary outcomes were urinary retention, length of stay, pain control, opioid consumption, and distance associated with physical therapy. Statistical analysis with univariate logistic regression was performed to evaluate the effect of anesthetic with primary outcomes.

Results: Patients undergoing TKA with mepivacaine had a shorter length of stay (28.1 ± 11.2 vs 33.6 ± 14.4 hours, $P = .002$) and fewer episodes of straight catheterization (3.8% vs 16.5%, $P = .021$) compared to bupivacaine. Patients administered mepivacaine exhibited slightly higher VAS pain scores and morphine consumption in the postanesthesia care unit (1.3 ± 1.9 vs 0.5 ± 1.3, $P = .002$; 2.2 ± 3.3 vs 0.8 ± 2.1 equivalents/h, $P = .002$), but otherwise exhibited no difference in VAS scores or morphine consumption afterwards. There was no need to convert to general anesthesia or transient neurologic symptom complication in either group.

Conclusion: Mepivacaine for spinal anesthesia with TKA had adequate duration to complete the surgery and facilitated a more rapid recovery with less urinary complications and a shorter length of stay. Patients administered mepivacaine did not display worse pain control or transient neurologic symptoms afterwards.

As the incidence of total knee arthroplasty (TKA) increases in this era of value-based care and bundled payments, improving early outcomes has become an important focus [1]. Historically, prolonged inpatient hospital stay after TKA was often related to pain, which was detrimental to a patient's time-to-ambulation and length of stay (LOS) [2,3]. Advances in anesthetic delivery and pain control have been paramount in improving hospital LOS. Although postoperative pain control has improved, there have been obstacles in implementing ambulatory TKA pathways secondary to the choice of spinal anesthetic. Issues such as prolonged motor blockade, altered proprioception, delayed ambulation, pain control, and urinary retention have been related to the choice of anesthetic [4–6].

Spinal anesthesia is often preferred given its low cost and rapid onset without the need for airway manipulation. Often attributed to less stress on the cardiopulmonary system, it has shown a decreased rate of adverse events compared to general anesthesia for joint replacement surgery [6–8]. The ideal spinal anesthetic agent has not been investigated or described in the setting of ambulatory TKA. Ideally, this agent would provide sufficient anesthesia for the duration of the procedure, a rapid return of motor, sensory, and bladder function afterwards and allow for early mobilization and safe discharge with a low risk of complications.

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Bupivacaine has been the gold standard for spinal anesthetic over the years due to its notable reliability and desirable side effect profile; however, its duration of action up to 3-9 hours may be too long for modern TKA [9]. Lidocaine has been gaining popularity as another option, but its length of action may be perceived as too short for some surgeons and many anesthesiologists have concerns about the reported frequency of transient neurological symptoms (TNS). Historically, lidocaine had nearly the highest incidence of TNS with relative risk rates greater than 7.0 compared to other anesthetics. These dreaded postoperative nerve pain issues precluded use of these shorter length spinal anesthetics decades ago. Mepivacaine, an anesthetic agent also popular in the 1980s, showed a decline in use in the 1990s after several studies again reported a high incidence of TNS [10], albeit lower than lidocaine. However, more recent larger studies have since refuted these findings and found similar rates of TNS [11] compared to the current gold standard. This agent has a desirable pharmacokinetic profile for usage in an ambulatory practice with an intermediate-acting duration (90-150 minutes) facilitating a faster recovery from induction, decreased urinary retention, and increased patient and surgeon satisfaction [9,10,12–14]. Mepivacaine has only been described for arthroscopic surgery in the current literature [13].

The purpose of this study is to investigate our early experience with mepivacaine and evaluate its safety and efficacy as a spinal anesthetic for rapid recovery in TKA. We hypothesized that mepivacaine would provide a safe, comfortable, and expeditious postoperative course with less urinary retention and improved postoperative outcomes as compared to the standard-of-care bupivacaine.

Materials and Methods

After receiving Institutional Review Board approval, the clinical records of consecutive patients who underwent unilateral TKA by a single fellowship-trained surgeon between November 2015 and July of 2016 were reviewed. All surgeries were performed at the same suburban teaching hospital. Patients were included in the study if they had undergone a unilateral TKA using either spinal mepivacaine or bupivacaine for primary osteoarthritis. Patients were excluded for history of postoperative nausea and vomiting, urinary retention, chronic narcotic use, and benign prostatic hyperplasia. These patients were excluded because they presented potential confounders to the results and could complicate the effect the spinal anesthetic had on a patient. After excluding patients who had revision procedures or general anesthesia, a total of 156 patients were included in the analysis.

After surgery, all patients were taken to the postanesthesia care unit (PACU), where initial opioid consumption and visual analog scale (VAS) pain scores were recorded by nursing staff blinded to the choice of anesthetic. All patients were compliant with a standardized preoperative pain and nausea protocol consisting of sustained-release morphine 15 mg, meloxicam 15 mg, and gabapentin 300 mg. Dexamethasone 8 mg was given intravenously after anesthetic induction for nausea and pain control. All patients received spinal anesthetic placed by the senior staff anesthesiologist. Choice of spinal anesthetic was dependent on the anesthesiologist randomly assigned to the room that day, as only half our staff had experience with mepivacaine and were comfortable using it regularly in this capacity. Dosing was based on height and weight per hospital protocol (Table 1). The standardized perioperative protocol did not include placement of a Foley catheter, as all patients had attempted to urinate in the preoperative holding area. Intraoperatively, a periarticular injection of 120 mL of diluted ropivacaine 300 mg with epinephrine 1 mg and ketorolac 30 mg was used for local administration. Intraoperative surgeon-delivered adductor canal blockade with 20 mL of the cocktail was added as previously described [15]. Postoperative pain regimen consisted of sustained-release morphine 15 mg every 8 hours for 24 hours, meloxicam 15 mg daily, gabapentin 300 mg twice a day, scheduled oral acetaminophen 975 mg every 8 hours, oral tramadol 50 mg every 6 hours, and oxycodone 5-10 mg as needed with morphine 1-2 mg intravenously as needed for breakthrough pain. A repeat dose of dexamethasone 8 mg intravenously was given again the morning after surgery. All patients were mobilized immediately after surgery. Patients were discharged home once they met minimum goals per institution physical therapy protocol.

Table 1
Mepivacaine and Bupivacaine Dosing.

Patient Height	Bupivacaine 0.75% Dose (mL)	Bupivacaine 0.75% Dose (mg)	Mepivacaine 2% Dose (mL)	Mepivacaine 2% Dose (mg)
Between 58 and 67 inches	1.4	10.5	3	60
>67 inches	1.6	12	3.4	68

Note: No additives (fentanyl or epinephrine) were added to any spinal dose. No patients under 4′10″ were encountered in the study.

Postoperative metrics were recorded by blinded inpatient nursing and physical therapy staff and included pain control, episodes of urinary retention, and TNS complaints. TNS was defined as new onset back pain or dysesthesia with radiation to the buttocks, hips, thighs, or calves occurring within the first 24 hours of surgery and lasting for 2-3 days [16,17]. Standard protocol for urination was patient due to void 6 hours after surgery. If not, a bladder scan was performed and straight catheterization performed if more than 240 mL of urine was present. Episodes of straight catheterization or Foley placement was used as the measurement for urinary complications, as we found documentation of incontinence to be variable. In our experience, we found that most retention occurred in men while incontinence was more of a problem with urinary dysfunction in women.

Pain control was evaluated through a 10-point VAS. Opioid consumption was converted to intravenous morphine equivalents for statistical analysis [18,19]. The initial phase of care, in the PACU, was defined as the time the patient arrived in the PACU to the time that the patient arrived on the floor. Postoperative day (POD) 0 was defined as the time the patient was admitted to an inpatient bed, until 0700 AM the following morning. POD 1 was defined as 0700 AM the day after surgery until 0700 AM the following day. Any additional PODs were similarly noted. During each phase, VAS scores were reported as averages. VAS scores were also recorded after each physical therapy session as an individual time point. Due to the variability of time each patient spent in a given phase of care, consumption of morphine equivalents was standardized to an hourly rate as validated in other studies [18,19].

Nausea and vomiting were assessed using the same phase of care definitions as described above. Per our institutional protocol, any individual episode of nausea is recorded in the medical record. Nausea was recorded in a binary fashion and any request for antinausea medication (ie, ondansetron) was also included as a surrogate. Discharge criteria were standardized among all patients, mainly walking >150 feet unassisted and negotiating stairs safely with no residual urinary or pain control concerns.

Statistical Analysis

All continuous variables are described using means and standard deviations, while all categorical variables are described using counts and percentages. Univariate 2-group comparisons were

Table 2
Demographic Data of Mepivacaine and Bupivacaine Groups.

	All Patients	Mepivacaine	Bupivacaine	*P* Value
Total				
Age [SD] (y)	65.6	65.0 (9.1)	65.9 (8.7)	.565
Gender				
Male	59	16	43	.159
Female	98	37	61	
Side				
Left (%)	70	22 (41.5%)	48 (46.1%)	.624
Right (%)	87	31 (58.5%)	56 (53.9%)	
Body mass index [SD]	33.1	32.4 (5.9)	33.5 (6.7)	.310
Operative time (min) [SD]	91.2	88.8 (15.4)	92.5 (14.3)	.221
ASA				
1-2	67	30	37	**.014**
3-4	89	23	66	

Bold values are statistically significant.
SD, standard deviation.

performed using chi-squared or Fisher's exact tests for categorical variables, and using 2-group t-tests or Wilcoxon rank-sum tests for continuous variables. Fisher's exact test was used when expected cell counts were <5 and Wilcoxon rank-sum tests were used when group sizes were small or when normality assumptions were violated. The odds of urinary retention are examined using a multivariable logistic regression model and results are presented as odds ratios with 95% confidence intervals. The effect of each variable on LOS is examined using a multivariable linear model and results are presented using beta estimates and their standard errors. Statistical significance is set at $P < .05$. All analyses are performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 156 consecutive patients were included in the study. The average age was 65.6 years old for all patients and the average body mass index was 33.1 (Table 2). Fifty-three patients were given mepivacaine anesthetic and 103 patients bupivacaine anesthetic.

Of the 156 patients, there were 19 episodes of straight catheterization (Table 3) with 2 episodes (3.8%) in the mepivacaine group and 17 (16.5%) in the bupivacaine group ($P = .021$). No patient in the mepivacaine group required an indwelling Foley; however, 2 patients in the bupivacaine group were discharged with Foley catheters ($P = .55$). In a multivariate analysis, women have significantly decreased odds of urinary retention when controlling for type of anesthetic used, age, gender, body mass index, and American Society of Anesthesiologist Physical Status Scale (ASA) score as one would expect (Table 4). Effect of spinal anesthetic showed a trend toward lower retention with mepivacaine at an odds ratio of 4.34, but did not reach statistical significance ($P = .19$) at current levels in this observational study.

The average LOS in the mepivacaine group was 28.1 hours, whereas the bupivacaine group required a half-day longer stay at 33.6 hours (Table 5, $P = .002$). When expressed as nights in the hospital, the average LOS in the mepivacaine group was 1.2 nights as compared to 1.4 nights in the bupivacaine group (Table 5; $P = .006$). A multiple linear regression model showed that patients administered bupivacaine had an average 0.3-day longer LOS compared to those administered mepivacaine (Table 6, $P = .002$). One patient in the mepivacaine group was discharged the same day as surgery. Although a significantly lower percentage of patients administered mepivacaine were ASA 3 or 4 as compared to bupivacaine (Table 2; 43.4% vs 64.1%, $P = .014$), a multiple linear regression model showed that ASA was not an independent predictor of LOS (Table 6).

The average PACU VAS pain scores were slightly greater in the mepivacaine cohort (Table 5; mepivacaine 1.3 vs bupivacaine 0.5; $P = .002$). There was no significant difference in pain control the night of surgery, POD 1, or throughout the remainder of the hospitalization (Table 5). The rate of morphine consumption was higher in the PACU for the mepivacaine group compared to the bupivacaine group (2.2 vs 0.8 morphine equivalents, $P = .002$); however, patients showed no increase during POD 1 or throughout the remainder of the hospitalization. There was no difference in physical therapist assessments of pain during therapy sessions.

There was no statistically significant difference in time to ambulation in patients given mepivacaine (8.7 ± 7.5 hours) or bupivacaine (8.3 ± 7.5 hours, $P = .629$). However, patients given mepivacaine anesthetic were able to walk longer distances with physical therapy on the day of surgery: POD 0 (Table 7) mean distances: mepivacaine 82 feet vs bupivacaine 53 feet, $P = .109$; POD 1 mean distances: mepivacaine 187.5 feet vs bupivacaine 163.3 feet, $P = .08$; however, these values were not statistically significant.

There were no cases of TNS observed in either group. No patients in either cohort required a blood transfusion. There was no difference in postoperative nausea, vomiting, or medication requests (Table 8). Neither group of patients required conversion to general anesthesia.

Table 3
Postoperative Urinary Retention.

	All	Mepivacaine	Bupivacaine	*P* Value
Straight catheterization				
Yes	19	2	17	**.021**
No	137	51	86	
Foley on discharge				
Yes	2	0	2	.548
No	154	53	101	

Bold values are statistically significant.

Table 4
Multivariable Model of Odds of Urinary Retention.

	Response	Odds Risk (95% CI)	*P* Value
Anesthetic	Bupivacaine vs mepivacaine	4.34 (0.49-38.22)	.186
Age		0.99 (0.90-1.08)	.765
Gender	Female vs male	0.06 (0.01-0.53)	**.011**
BMI		0.93 (0.81-1.05)	.240
ASA	1-2 vs 3-4	0.43 (0.10-1.96)	.277

Bold values are statistically significant.
CI, confidence interval; BMI, body mass index.

Table 5
Postoperative Pain Assessments and Length of Stay.

	All	Mepivacaine	Bupivacaine	*P* Value
Time in PACU (h)	1.8 ± 0.7	1.9 ± 0.7	1.7 ± 0.6	.083
Total length of stay (h)	31.7 ± 13.6	28.1 ± 11.2	33.6 ± 14.4	**.002**
Total length of stay (d)	1.3 ± 0.6	1.2 ± 0.5	1.4 ± 0.6	**.006**
Pain (VAS)				
PACU	0.8 ± 1.6	1.3 ± 1.9	0.5 ± 1.3	**.002**
POD 0	2.3 ± 1.6	2.5 ± 1.6	2.2 ± 1.6	.248
POD 1	2.5 ± 1.9	2.4 ± 2.0	2.5 ± 1.9	.592
POD 2	3.3 ± 2.5	2.6 ± 2.8	3.5 ± 2.4	.273
POD 3	4.0 ± 1.5	5.0 ± 0	6 3.8 ± 1.5	.478
Morphine usage (equivalents/h)				
PACU	1.3 ± 2.7	2.2 ± 3.3	0.8 ± 2.1	**.002**
POD 1	1.0 ± 0.5	1.0 ± 0.5	1.0 ± 0.5	.544
POD 2	1.5 ± 1.6	1.1 ± 1.3	1.6 ± 1.7	.393
POD 3	6.8 ± 14.2	2.4 ± 0	7.6 ± 15.4	.482

Bold values are statistically significant.

Table 6
Multiple Linear Regression Showing Effect of Variables on Length of Stay.

	Response	Estimate	*P* Value
Anesthetic	Bupivacaine vs mepivacaine	0.30 ± 0.10	**.002**
Age		0.01 ± 0.01	.159
Gender	Female vs male	0.16 ± 0.10	.084
BMI		0.003 ± 0.01	.649
ASA	1-2 vs 3-4	0.02 ± 0.09	.868

Bold values are statistically significant.
BMI, body mass index.

Discussion

Our study found that patients undergoing TKA under mepivacaine spinal anesthetic had improvements in LOS and urinary retention. Bupivacaine and mepivacaine showed equivalent pain control, TNS rates, ambulation distances, transfusion rates, nausea, vomiting, and requests for nausea medication. Given the more desirable duration of action, our study suggests that mepivacaine has multiple advantages and few drawbacks compared to bupivacaine as a spinal anesthetic in ambulatory TKA.

Much of the cost for TKA is derived from a patients' LOS. In the past 3 decades, the LOS has decreased from a mean of 3 weeks to approximately 3 days, with patients potentially being discharged the same day as surgery [1,20]. Previous studies have shown no difference in complications between a short LOS compared to a long LOS after a TKA [21,22]. In our study, patients treated with mepivacaine had approximately a 5-hour, or 17%, decrease in LOS compared to patients treated with bupivacaine, despite the fact that there was no statistically significant difference in time-to-ambulation between the cohorts. Therapist availability likely had a more significant role in time to ambulation. While this may suggest that patients were able to ambulate at similar times postoperatively, their mobilization potential as seen in distance walked likely helped propel an early discharge that is a multifaceted process. This was further validated by a multiple linear regression model which showed that the type of anesthetic used was an independent predictor of LOS, with patients administered mepivacaine having a 0.3-day shorter LOS as compared to bupivacaine. While numerically 5 hours is not much, in practicality it is the difference between a morning and afternoon discharge at many institutions. For many patients, this could improve the chances of same-day discharge. Clinical pathways that emphasize pain control, improved nausea prevention, and earlier patient mobilization continue to evolve. Advances in preoperative optimization, patient selection, surgical techniques, and pain control have made incremental improvements, so the proper choice of anesthetic may be the remaining integral component to enable rapid recovery after total joint arthroplasty. It should be noted that although a higher percentage of patients administered mepivacaine were healthier based on ASA scores, a multivariate analysis revealed that ASA scores were not an independent predictor of LOS. Mepivacaine as a spinal anesthetic shows promise as an ideal anesthetic to achieve same-day discharge after TKA.

Table 7
Physical Therapy Performance and Pain.

	All	Mepivacaine	Bupivacaine	*P* Value
Time to ambulation (h)	8.4 ± 7.5	8.7 ± 7.5	8.3 ± 7.5	.629
Distance with PT (feet)				
POD 0	62.6 ± 64.3	82.0 ± 86.7	53.0 ± 47.3	.109
POD 1	171.5 ± 86.4	187.5 ± 89.1	163.3 ± 80.1	.080
POD 2	162.1 ± 78.0	155.0 ± 71.6	69.5 ± 67.9	.738
POD 3	69.5 ± 67.9	-	15 ± 0	.738
Pain with PT (VAS)				
POD 0	3.1 ± 2.3	3.0 ± 2.1	3.1 ± 2.4	.896
POD 1	2.8 ± 2.3	2.6 ± 2.3	2.9 ± 2.4	.470
POD 2	3.9 ± 2.8	3.4 ± 3.6	3.9 ± 2.7	.756
POD 3	4.8 ± 1.8	-	4.8 ± 1.8	.756

PT, physical therapy.

Table 8
Postoperative Nausea and Vomiting.

	All	Mepivacaine	Bupivacaine	*P* Value
Nausea				
POD 0				
Yes	18	7	11	.792
No	138	46	92	
POD 1				
Yes	5	3	2	.338
No	151	50	101	
Vomiting				
POD 0				
Yes	13	7	6	.133
No	143	46	97	
POD 1				
Yes	5	3	2	.338
No	151	50	101	
Ondansetron requested				
Yes	19	9	10	.204
No	137	44	93	

There is a long-held belief that mepivacaine is associated with increased TNS symptoms, as high as 37% [10]. It has been conjectured that the reason TNS symptoms were high in the 1990s were due to higher, nonstandardized concentrations, older preservatives, and antiquated purification methods [17]. Several studies have shown that contemporary formulations of mepivacaine have TNS rates as low as 0%-7.4%, which is similar to the rate of TNS in the standard bupivacaine preparation, and a lower incidence than reported rates with lidocaine [23]. Our study found no incidence of TNS in either the mepivacaine or bupivacaine group, consistent with the previous study by Pawlowski et al [24] that evaluated 38 patients undergoing arthroscopic orthopedic surgery. The modern-day safety profile of mepivacaine in similar applications has also been reproduced by several other studies [13,24].

Although our study showed that significantly fewer patients in the mepivacaine group had urinary retention compared to those with bupivacaine, a multivariate analysis of this cohort suggests that the type of anesthetic used was not an independent predictor of urinary retention; a trend was noted with odds ratio of 4.34, although our data suggest that this is likely a multifaceted problem. Urinary retention has been shown to be a risk factor for postoperative urinary infection as well as readmission and increased LOS [1]. The ability to urinate has been documented to return approximately 15 minutes after return of motor and sensory function after spinal anesthesia, with a complete return of spontaneous urination occurring 1-3.5 hours after ambulation on average [25]. The detrusor muscle, responsible for the ability to urinate, is one of the last muscles to return after spinal anesthesia [25]. It has been shown in multiple studies that use of long-acting anesthetics increases the incidence of postoperative urinary retention [25]. The opposite has also been shown with the time to void after short-acting local anesthetics, such as mepivacaine. The result of faster regression of sensory and motor block leads to a more rapid recovery of bladder function [12,26,27]. This is consistent with our findings of decreased need for straight catheterization among patients receiving mepivacaine spinals. Moreover, urinary retention has been shown to correlate with higher rates of bacteriuria [28,29]. The chances of deep infection have been reported to increase 3-6 times if postoperative bacteriuria is present, and hematogenous spread of urinary organisms has been reported,

further emphasizing the importance of postoperative urinary control [30–34].

The most common impediments to discharge of modern-day arthroplasty have been delays in mobilization, functional recovery, and pain control. With a shorter duration of action, earlier rebound pain has been a concern with the shorter anesthetics. This was reflected in our data, as early morphine consumption was 1.4 morphine equivalents/h greater in the mepivacaine group compared to bupivacaine. Based on our 10-point VAS scale, patients given mepivacaine had a statistically significant 0.8 point increase in pain compared to bupivacaine in the PACU; however, this is not clinically significant based on previously published minimal clinically important difference for VAS scores in patients undergoing TKA [35]. By the time patients were admitted to the inpatient floor, however, the VAS scores and rate of morphine consumption were not statistically significant. When using a multimodal pain regimen, our patient population experienced only mild average pain levels regardless of anesthetic choice.

Limitations

The retrospective nature of this study presents the main inherent limitation. Due to the historical concerns surrounding mepivacaine, many anesthesiologists at our institution refused to administer mepivacaine if they had not had prior experience with it. This did provide a unique opportunity to essentially randomize from day to day, as those with experience decades ago were comfortable using it on all eligible patients. Although all postoperative metrics were authored by blinded staff following the same institutional protocols, there is some variability among different nursing and therapy staff as in any hospital. Ideally, a study would have the same nurse and therapist for all patients to create a more reproducible gradient of responses. Therapist availability and timing factor into LOS. Patients with a history of postoperative nausea and vomiting, urinary retention, chronic narcotic use, and benign prostatic hyperplasia were excluded from the study during the data collection process, and it is not known how many of these patients were excluded in each cohort. Patients with these comorbidities are inherent in any arthroplasty practice and this could have presented a potential confounder to the data. Moreover, urinary incontinence was variably documented, as all women initially wore briefs for incontinence but documentation of saturation was lacking. As more urinary dysfunction via retention in predominantly men was noted in the bupivacaine group, it is reasonable to assume that dysfunction incidence would be higher had true incontinence also been included. It should also be noted that while benign prostatic hyperplasia was an exclusion criteria, it is impossible to account for previously undiagnosed cases that may have required additional episodes of straight catheterization or Foley placement. The preponderance for gender-related variability should have been evenly distributed as the demographics illustrated similar cohorts. Given all these recovery factors theoretically relate directly to length of anesthetic duration, a randomized, prospective trial will be needed to specifically evaluate the duration of action of mepivacaine in this surgical population.

Conclusions

Our study found that patients undergoing TKA with mepivacaine spinal anesthetic had a more rapid recovery after TKA compared to bupivacaine as seen by improved urinary function and a shorter LOS. These patients exhibited similar pain and nausea control without an incidence of TNS complication.

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