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Fentanyl with low dose bupivacaine (isobaric and hyperbaric) and levobupivacaine for combined spinal-epidural technique in cesarean section

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Abstract

To compare the hemodynamic and motor block effects of fentanyl combined with low doses of isobaric and hyperbaric bupivacaine and isobaric levobupivacaine in Caesarean operations with Combined Spinal-Epidural Anesthesia (CSEA) method. The aim of study is to use levobupivacaine and bupivacaine more effectively and comfortably in caesarean sections. Methods: A hundred and sixty pregnant women were randomly divided into four groups (n=40). A total volume of 1.8 mL containing 9 mg of plain bupivacaine (Group A), 5 mg of plain bupivacaine plus 40 µg fentanyl (Group B), 5 mg of plain levobupivacaine plus 40 µg fentanyl (Group C) and 5mg of hyperbaric bupivacaine plus 40 µg fentanyl (Group D) were applied. Results: Hemodynamic parameters and level of sensory block did not differ among the groups. Time to reach T4 sensory block level was 6 ± 1 min for Group A, 4 ± 1 min for Group B and C, and 7.5±2.5 min for Group D (P= 0.045). Bromage scores were: 110.5 ± 10.1 min, 90.1 ±11.1 min, and 85.1 ± 10.2 min for Group A, B and D, respectively. The patients in Group C had no motor block. Conclusions: Combining fentanyl (40 µg) with low dose (5 mg) isobaric and hyperbaric bupivacaine, and isobaric levobupivacaine provided sufficient anesthesia. Sensory block with no motor block was provided by adding fentanyl, especially to levobupivacaine, which eases perioperative period and delivers patient comfort.

Keywords: Fentanyl, low doses, bupivacaine, levobupivacaine, Cesarean

Introduction

In cesarean section, spinal anesthesia has the advantage of being a simple technique that can be performed with predictable risks [1]. However, when administered in excessive doses, intrathecal local anesthetics may induce motor blockade and hypotension, along with sensory blockade. On the other hand, utilization of opioids in Combined Spinal-Epidural Anesthesia (CSEA) can reduce the dose of local anesthetics, which improves analgesia through exerting a synergistic effect.

The use of opioids along with low doses of local anesthetics decreases the incidence of local anesthetic related side-effects, shortens the time of onset of anesthesia, and increases the quality of intra- and post-operative analgesia [2].

Fentanyl is an opioid commonly used in obstetrics. Morphine, a hydrophilic drug, may cause delayed respiratory depression by reaching opioid receptors in the respiratory center in the fourth ventricle; the greater lipid solubility of fentanyl in comparison with morphine makes it suitable for continuous epidural infusion [3].

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Levobupivacaine is the S-(-)-enantiomer of racemic bupivacaine and is considered a safe alternative to bupivacaine in spinal anesthesia in obstetrics [4-5]. At equal concentrations, levobupivacaine is less toxic to the central nervous system and cardiovascular system than bupivacaine. Moreover, levobupivacaine causes less motor blockade and hypotension as compared to bupivacaine [5-6]. It has more specific effects on sensory rather than motor nerve fibers. Achieving a prolonged sensory blockade and faster mobilization in association with faster recovery from motor blockade without experiencing hypotension by levobupivacaine is pertinent to obstetric surgery and patients.

It was hypothesized that utilization of fentanyl with levobupivacaine and bupivacaine would improve the quality of anesthesia and patient satisfaction by preventing hemodynamic instability or sensation of paralysis that patients fear. Therefore, this study was conducted to evaluate the maternal clinical effects of fentanyl and low doses of levobupivacaine and bupivacaine (isobaric and hyperbaric) combination.

Mareial and Methods

Study population

The study protocol was approved by the Ethics committee of

Atatürk University Faculty of Medicine (24.06. 2011, protocol number: 61) and written informed consents were obtained from all participants. A hundred and sixty ASA I and II patients, over the age of 18, weighing 50-100 kg were randomly assigned to four groups. Patients with hypotension, neurological diseases, infection at the entry site, known allergies to local anesthetic drugs and patients receiving antithrombotic treatment, and those with alcohol or drug addictions were excluded from the study.

Study design

After intravenous prehydration with 500 mL of Ringer's lactate solution, hemodynamic variables including electrocardiography (ECG), systolic and diastolic blood pressure, heart rate, and peripheral oxygen saturation (SpO2) were monitored.

Combined spinal-epidural catheters (Combifix Standard, Egemen International, Balçova, Izmir, Turkey) were inserted into intervertebral spaces between the L2 and 3 or L3 and 4 in all patients. After L2-3 or L3-4 spaces were located, the skin was cleaned with antiseptic solutions, and local anesthesia was performed in sitting position. 18-G Tuohy epidural needle was advanced along the midline, the epidural space was identified by loss of resistance technique. After CSF flow was seen in the 27 G pencil point spinal needle, the fluid was injected into the subarachnoid space. A total volume of 1.8 mL were applied in all groups; patients in Group A received 1.8 mL of (5 mg/mL) plain bupivacaine (Marcaine vial 20 mL, Astra Zeneca, Istanbul, Turkey); patients in Group B were administered with 1 mL of (5 mg/dL) plain bupivacaine plus 40 µg fentanyl (Fentanyl, Abbott, North Chicago, IL); patients in Group C were administered with 1 mL of (5 mg/dL) plain levobupivacaine (Chirocaine, Abbott, North Chicago, IL) plus 40 µg fentanyl; and patients in Group D received 1 mL of (5 mg/mL) hyperbaric bupivacaine (Marcaine heavy 0.5%, 4 mL, Astra Zeneca, Istanbul, Turkey) plus 40 µg fentanyl.

Data collection

The patients were positioned in a left lateral recumbent position with 15 degrees. Heart rate (HR), blood pressure (BP), and peripheral oxygen saturation (SpO2) were monitored. Sensory block level was assessed bilaterally using the hot-cold test at the mid-clavicular line and the values were recorded at 0, 1, 3, 5, 7, 9, 12, 15, 30 minutes and the recording time was extended to 1 or 2 hours, relative to surgical intervention. Time to peak sensory block, time to reach T4 sensory level (targeted), time to regression of sensory block, time to regression to T10, and regression of sensory block level were assessed at 1 and 2 hours after surgery. The modified Bromage Scores (BS) were recorded at 0, 1, 3, 5, 7, 9, 12, 15, 18, 21, 24, 27, 30, 35, 40, and 45 minutes and the recording time was extended to 1 or 2 hours, relative to surgery. The modified BS was scored as 0, 1, 2, and 3, if the patient had no motor block, if the patient could not raise her leg in extension position, if the patient could not bend her knees, but could move her feet, and if the patient could not move feet, respectively. E3 The time of onset of motor block was defined as the interval between intrathecal administration and BS of 1. The duration of sensory or motor block was defined as the interval from intrathecal administration to the T10 regression time or to the time at which the BS returned to zero.

Side effects such as hypotension, bradycardia, nausea, and vomiting were recorded. Hypotension was defined as a >20% decrease in mean arterial pressure from baseline level and was treated with 5 mg of intravenous ephedrine. Bradycardia was defined as a pulse rate of <50 beats/min and was treated with 0.5 mg intravenous atropine. Patients having persistent nausea or vomiting were treated with 4 mg intravenous ondansetron.

Complaints of pain and patient satisfaction were assessed and recorded in the postoperative period using the Verbal Rating Scale (VRS) (from 0 = no pain to 10 = the worst pain imaginable) and the Satisfaction Score (1 = poor, 2 = moderate, 3 = well, 4 = perfect). The time to first rescue analgesia was defined as the time the VRS of the cases was 3 or higher. Moreover, the APGAR score (at 1 and 5 min), patient comfort, and surgical satisfaction were recorded. All assessments were made by independent anesthetists blinded to both the anesthetic technique and anesthetic drug used for each patient. The density of the drugs was measured at room temperature using an automatic urine analyzer.

Statistical analysis

The primary outcome was the incidence of hypotension during surgery. To achieve a statistical significant difference of 40% in the incidence of hypotension between the groups at α error of 0.05 and power of 95%, 36 patients were needed. The data were subjected to one-way ANOVA (SPSS 18.0, Chicago, IL). The categorical data for possible associations were cross-tabulated in the Chi-Square test. The group mean differences were attained using the post-hoc Bonferroni correction. Statistical significance was set at $P < 0.05$. The results were expressed as least square means with standard deviations.

Results

Demographic data and surgical characteristics were similar in all groups (Table 1). No complications related to the procedure, i.e. vaso-vagal syncope, hematoma, and local anesthetic toxicity were observed. All groups had similar baseline systolic blood pressure (SBP) and HR values (Figure 1). Surgery was performed when the sensory block level reached T4 level. The time until the sensory block reached T4 was the highest in Group D as compared to the other groups (P= 0.013). The time between spinal puncture and the start of surgery was also the longest in Group D (p= 0.013) (Table 2). At one hour postoperatively, there was no difference in the regression of sensory block (sensory level <T10) among the groups (P= 0.23). The frequency of patients with sensory block level lower than T10 in Group A was greater than that in the other groups in the postoperative second hour (P= 0.000).

Table 1. Anthropometric characteristics of the patients

Variable	Group A (n=40)	Group B (n=40)	Group C (n=40)	Group D (n=40)
Age (years)	29.6±5.8	31.9±5.8	30.6±5.5	30.5±5.9
Height (cm)	160.7±4.8	158.4±3.9	159.6±4.9	158.8±4.9
Weight (kg)	80.0±8.9	75.8±7.6	76.7±6.9	76.9±7.7
Duration of surgery (min)	46.0±7.8	46.0±8.8	48.0±8.9	47.0±7.8
L3-L4	21	19	20	19
L4-L5	19	21	20	21

Data are presented as mean±standard deviation and number, where appropriate. There was no statistically significant difference between the groups (P>0.05).

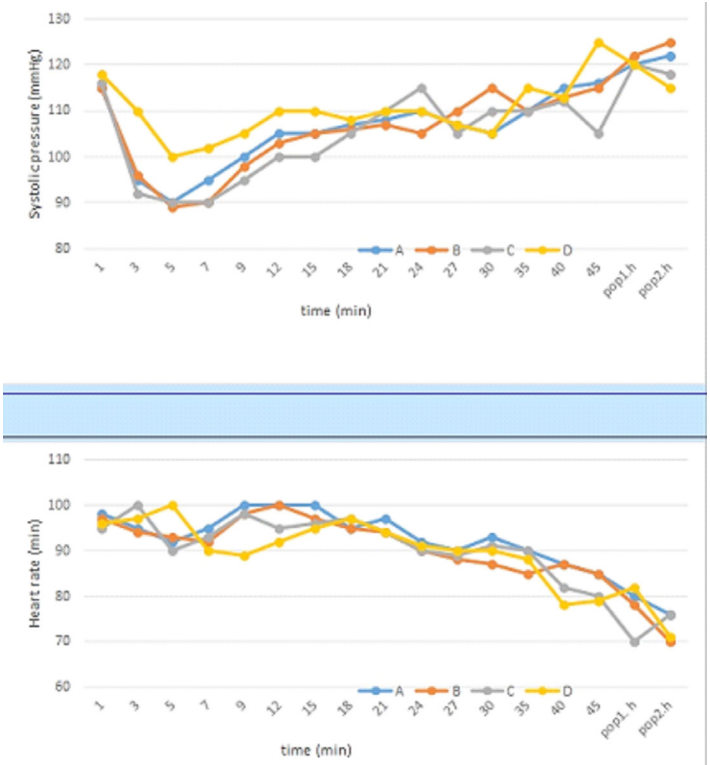

Figure 1. Systolic blood pressure (upper panel) and heart rate (lower panel) of the patients according to study groups. There was no statistically significant difference between the groups (P>0.05).

There was no difference in execution time defined as the time from skin incision to closure of the skin among the groups (P= 1.000) (Table 2).

Table 2. Surgical parameters and APGAR scores of the study groups

Variable	Group A (n=40)	Group B (n=40)	Group C (n=40)	Group D (n=40)
Time to sensory block T4 (min)	4±2	3±2	3±2	6±3*
Peak sensory level	T2 (T2-T3)	T2 (T2-T3)	T2 (T2-T3)	T2 (T2-T3)
Peak sensory time (min)	8±4	10±5	10±5	11±4
Time to Regression Br0 (min)	110.50±10.07	90.10±11.12	No motor blockα	85.12±10.23
Time to Regression T10 (min)	85±10.7	91.10±10.12	100±12.1	95±9.8
First analgesic need (VRB=3) (min)	39±17.65***	129.38±10.8	132.4±15.41	128.5±14
The duration to begin surgery (min)	5	5	5	5.35**
Apgar score (min 1)	8 (7-9)	8 (7-9)	8 (7-9)	8 (7-9)
Apgar score (min 5)	9 (8-10)	9 (8-10)	9 (7-10)	9 (8-10)
Mean ephedrine dose (mg)	4.2±4.1∞	2.2±1.1	2.4±1.2	2.7±1.3
Mean ephedrine dose (mg)	4.2±4.1∞	2.2±1.1	2.4±1.2	2.7±1.3

Data are presented as mean±standard deviation and (minimum-maximum), where appropriate.
*The time to reach T4 for Group D was longer than that for the other groups (P= 0.045).
α Lack of motor block in Group C (P= 0.000).
***The time to first analgesic need was shorter in Group A than the other groups (P=0.000).
**The time to begin surgery was significantly longer in Group D than that for the other groups (p= 0.01).
∞ Ephedrine dose was higher in Group A than that in the other groups at 3 minutes. (p= 0.01).

There was no significant difference among the groups in respect to the quality of analgesia (p= 0.267). None of the cases experienced pain during incision, neither required analgesics intravenously or through the epidural catheter. Moreover, the need for sedation was similar across the groups (P= 0.243). Eight patients in group A, 7 patients in group B, 9 patients in group C, and 8 patients in group D received sedation.

There were significant differences in the Bromage scores and sensory block levels among the groups (P= 0.000-0.041). The Bromage score was 3 in group A, and 2 in group B and D. In group C, the Bromage score was 1 in 9 patients and became 0 after 35 minutes. The Bromage score was 0 in the remaining patients in group C (n= 31) (Figure 2). The faster regression of Bromage score in group B and D in comparison with group A at 1-hour postoperatively was considerable (P= 0.000). At 2-hours postoperatively, only the patients in group A had Bromage scores higher than 0 (P= 0.035).

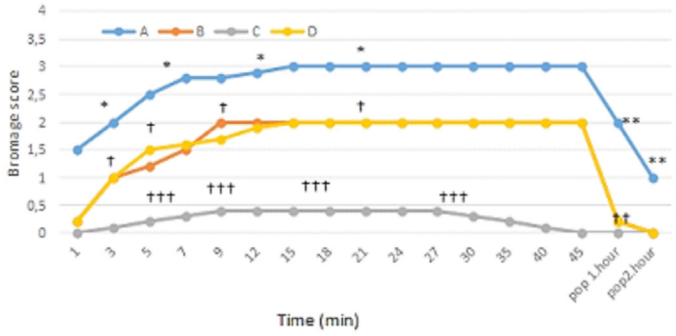

Figure 2. Bromage scores of the patients.

*A more intense motor block was observed in group A, when compared to the other groups (P= 0.01).

**Prolongation in motor block regression in group A was significant (P= 0.000).

† A more intense motor block was present in group B and C when compared to group A (P= 0.041).

†† Motor block regression was significant in group B and C when compared to group A (P= 0.000).

††† Lack of motor block in group C was significant when compared to the other groups (P= 0.000).

Eight patients in group A had nausea at 3 minutes (P= 0.014) (Table 3). Vomiting occurred in 2 patients in group A at 7 minutes. However, there was no statistically significant difference between the groups (P= 0.057). Sixteen patients in group A had hypotension at 3 minutes (P= 0.01). Pruritus was present in all cases (more than 90%), except for the patients in Group A (P= 0.000).

Patient satisfaction in group C was significantly greater than that in the other groups (Table 4). Total dose of ephedrine and the number of patients who received atropine were similar at all measurement times, except the measurement taken at 3 minutes.

Group A required a higher dose of ephedrine than the other groups at 3 minutes (P= 0.010). Finally, only the density of hyperbaric bupivacaine and hyperbaric bupivacaine plus fentanyl was significantly higher than that of the other groups (Table 5).

Table 3. Side effects observed in the study

Variable	Group A n (%)	Group B n (%)	Group C n (%)	Group D n (%)
Hypotension	24 (60)∞	15 (37)	12 (30)	12 (30)
Nausea	8 (20)*	2 (5)	2 (5)	2 (5)
Vomiting	2 (5)	-	-	-
Pruritus	0	36 (90)	35 (88)	35 (88)

*The frequency of nausea was higher in Group A than that in the other groups at 3 minutes (P= 0.014).
∞ The frequency of hypotension was higher in Group A than that in the other groups at 3 minutes (P=0.01).

Table 4. Patient satisfaction levels ibn the study groups, n (%)*

Group	Level				P value
	Poor n (%)	Moderate n (%)	Good n (%)	Perfect n (%)	
A		4 (10)	3 (7)	33 (82)	0.101
B	-	3 (7)	4 (10)	33 (82)	0.090
C	-	1 (2)	5 (12)	34 (85)	0.035*
D	-	2 (5)	10 (25)	28 (70)	0.111

* Patient satisfaction in Group C was higher than that in other groups (P= 0.035).

Table 5. Density of the drugs and drug combinations

Group	Concentration	Density (g/mL)
Plain bupivacaine	0.5%, 5 mg/mL	1.005
Levobupivacaine	0.5%, 5 mg/mL	1.006
Hyperbaric bupivacaine	0.5%, 5 mg/mL	1.022*
Fentanyl	50 µg/mL	1.004
Plain bupivacaine + fentanyl	5 mg + 40 µg	1.004
Levobupivacaine + fentanyl	5 mg + 40 µg	1.005
Hyperbaric bupivacaine + fentanyl	5 mg + 40 µg	1.011*
Cerebrospinal fluid	1.8 mL	1.003

*The densities of hyperbaric bupivacaine and hyperbaric bupivacaine + fentanyl were higher than others.

Discussion

The present study showed that the use of 40 µg fentanyl with 5 mg plain bupivacaine, hyperbaric bupivacaine, and 5 mg plain levobupivacaine provided effective anesthesia. The incidence of hypotension was the highest when plain bupivacaine (9 mg) was used alone. Combination of fentanyl with levobupivacaine induced less motor blockade than hyperbaric and isobaric bupivacaine. Lack of motor blockade and sufficient sensory block are two important determinants of patient satisfaction.

The efficacy of neuraxial local anesthetics is enhanced by the addition of intrathecal opioids. Such combinations are usually associated with improved anesthesia and analgesia. It also allows the use of very low doses of local anesthetics, which contributes to more stable hemodynamics. In the present study, high sensory levels (T2) of anesthesia was achieved in the early period in the patients administered with fentanyl plus bupivacaine or levobupivacaine and in the late period in the patients administered with fentanyl plus hyperbaric bupivacaine. No additional dose of epidural drugs was given in any of the patients.

Sen et al [7]. reported that the speed of onset and offset of motor and sensory block was faster for hyperbaric levobupivacaine than that for isobaric levobupivacaine when administered at equal doses. While short lasting motor block is advantageous in short operations, the operations may be difficult in the hands of inexperienced obstetricians. In the study of Gautier et al [5], effective anesthesia was achieved in great majority of patients who received 8 mg levobupivacaine plus 2.5g sufentanil. Guasch et al. determined that the requirement for rescue analgesia was higher in the group receiving 5 mg of levobupivacaine with 25 µg fentanyl [8]. The dose of fentanyl used in our study was higher; this may explain the achievement of effective anesthesia and analgesia without needing supplemental epidural medication. Goyal et al. administered 10 mg of 0.5% levobupivacaine and 0.5% hyperbaric bupivacaine in combination with 25 µg fentanyl for spinal anesthesia in patients undergoing CS, and found that levobupivacaine produced adequate and comparable sensory blockade, but less motor blockade than bupivacaine 3. Turkmen et al. reported that motor block level was lower, whereas duration of analgesia was longer and maximal sensory block level was higher in the patients who received 15 µg fentanyl plus 7.5 mg levobupivacaine than 15 µg fentanyl plus 7.5 mg bupivacaine [9].

The results of the present study are similar to those reported in prospective randomized, double-blind studies done by Guler et al. [10]. and Duggai et al [11]. In both these studies, 10 mg levobupivacaine with fentanyl was compared to 10 mg bupivacaine with fentanyl. Guler et al. concluded that the use of levobupivacaine was advantageous due to significantly shorter and less pronounced motor blockade along with better hemodynamic stability than racemic bupivacaine [10]. Duggai et al. went further to conclude that levobupivacaine should be the preferred alternative to bupivacaine in patients undergoing elective cesarean section 11. In the current study, the use of a higher dose of fentanyl and a lower dose of levobupivacaine might have contributed to achieving effective anesthesia and analgesia, and less pronounced motor blockade.

Although the incidence of visceral pain is lower with higher doses, it may cause a delayed block effect. The need for analgesics regardless of the sensory level is linked to the fact that visceral pain follows different paths in the upper thoracic cord. Visceral pain travels through demyelinated C fibers that are not blocked by the presence of low concentrations of local anesthetics. Bogra et al. reported that bupivacaine -fentanyl combination resulted in abolishment of visceral pain, reduction in nausea incidence, improved hemodynamic stability and longer duration of post-operative analgesia [12]. In agreement with the study of Bryson et al., complete motor block was achieved along with adequate analgesia and patient satisfaction by using fentanyl plus low dose bupivacaine [13].In the fentanyl combination groups, in addition to the improvement in the quality of analgesia, the time to first analgesic requirement was also prolonged.

Addition of 25, 15, and 10 µg fentanyl to 5, 7.5, and 10 mg bupivacaine was reported to deliver an analgesia success rate of 60, 82.5, and 100% respectively [14].Effective analgesia could not

be achieved, although the incidence of side effects is lower at lower doses. Despite utilization of 5 mg of bupivacaine, achievement of satisfactory analgesia can be the result of using a higher dose of fentanyl in the present study. It appeared that the frequency of hypotension and the need for additional doses of ephedrine was related to the usage of hyperbaric form and higher dose of bupivacaine without fentanyl. The degree of sympathetic block affects the severity and duration of hypotension. When the drug concentration penetrating the nerves (proportional to anesthetic solution concentration) is reduced, sympathetic block becomes less intense [15]. Intrathecal anesthesia may cause unwanted side effects such as nausea and vomiting during peritoneal traction. Despite the block that reaches to the level of T4 segment, patients may experience distress caused by visceral traction, particularly during uterine exteriorisation. Except for 2 patients, vomiting was not noted in the fentanyl groups. This positive effect of fentanyl was attributed to prevention of autonomic responses. In the study by Karaman et al. that compared the effects of intrathecal fentanyl and morphine, it was shown that the incidence of nausea and vomiting was lower in the fentanyl group than that in the morphine group [16]. Ben-David et al. also reported that the incidence of hypotension, nausea, and vasopressor need in the patients administered with 10 mg bupivacaine alone were higher than that in the patients administered with 5 mg bupivacaine plus 25 µg fentanyl [17].

Another common side effect of intrathecal opioid use is pruritus. It develops in 50% to 90% of the patients at various degrees. Pruritus due to highly lipid soluble opioids is temporary; however, severe and long lasting pruritus may develop due to intrathecal morphine use. The mechanism of facial pruritus is not linked to histamine release, but is directly caused by opioid receptor effect in the medulla [16]. The distribution of pruritus is segmental in the other areas, and is correlated with the degree of analgesia. In our study, pruritus was seen in 90-95% of the patients in the fentanyl group, mostly in the facial area, and did not require treatment. However, we observed that pruritus disappeared completely in the patients upon sedation by propofol administration. As pruritus started at 9 to 15 minutes of intrathecal drug delivery, low-dose propofol sedation could be used in that period as this interval coincides with the delivery of the baby.

Conclusion

In the CSEA technique applied in Caesarean cases, sufficient anesthesia was achieved by adding fentanyl (40 µg) to low dose (5 mg) isobaric and hyperbaric bupivacaine, and levobupivacaine. Fentanyl usage considerably reduced the frequency of hypotension and the dose of anesthetics. Combining fentanyl with levobupivacaine resulted in lack of motor blockade and rapid regression, which improved patient comfort and satisfaction. Further research is required to investigate the measurements and the effects of the ideal dose, density and baricity of intrathecal local anesthetics administered.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
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