

A Comparison of Morphine, Meperidine, and Oxymorphone as Utilized in Patient-controlled Analgesia Following Cesarean Delivery

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Seventy-five patients (n = 75) undergoing elective cesarean delivery during epidural anesthesia were randomly assigned to receive one of three opioid analgesics *via* patient-controlled analgesia (PCA) when they first complained of pain in the recovery room. Following administration of an analgesic loading dose, patients were allowed to self-administer morphine 1.8 mg, meperidine 18 mg, or oxymorphone 0.3 mg iv every 8 min as required. Data collected during the 24-h observation period included visual analog scale (VAS) pain scores at rest and during movement, VAS patient satisfaction scores, total drug administered, the ratio of attempts/injections, and the incidence of nausea/vomiting, sedation, and pruritus. After adjusting for narcotic potency, no differences in 24-h dose requirements were noted between treatment groups (NS). All patients achieved an excellent level of analgesia at rest (NS); however, onset was most rapid with oxymorphone ($P < 0.05$). The percentage of patients reporting severe pain during movement was highest in the meperidine group ($P < 0.05$). Oxymorphone was associated with the highest incidence of nausea and vomiting ($P < 0.05$), whereas increased sedation and pruritus were noted with morphine. Patient satisfaction with drug effect demonstrated significant negative correlations with resting pain scores and degree of sedation. Whereas morphine is a more commonly utilized PCA analgesic, the excellent analgesia, low incidence of sedation, and high patient satisfaction provided by meperidine and oxymorphone suggested useful alternatives. (Key words: Analgesics, opioids: morphine; meperidine; oxymorphone. Anesthesia, obstetric: cesarean delivery. Pain: postoperative. Patient-controlled analgesia.)

MORPHINE is commonly employed for patient-controlled analgesia (PCA)¹; however, a recent evaluation in patients following cesarean delivery raised questions as to whether it was the optimal analgesic for use in this setting. Harrison *et al.*² reported that delay in onset and peak analgesic effect with morphine resulted in high 24-h PCA dose requirements and no significant improvement in pain scores when compared with individuals treated with im administered narcotic. Analgesics having more rapid onset and

a low incidence of adverse effects may offer advantages when utilized in PCA,^{3,4} whereas ultrashort duration opioids are less effective.⁵ In this regard, meperidine has become an important PCA agent in many European centers.^{6,7} The pharmacologic profile of oxymorphone, specifically its potent analgesic effect,⁸ low level of sedation,⁹ and negligible release of histamine,¹⁰ also suggested useful application in PCA. Oxymorphone was recently found to provide high patient satisfaction and five to six times the analgesic potency of morphine when self-administered by women recovering from cesarean delivery¹¹ and major orthopedic procedures. §

No previous PCA study has attempted to compare analgesic efficacy, patient satisfaction, and adverse effects provided by different opioid compounds in individuals exposed to similar forms of postsurgical pain. Consequently, we examined in a prospective double-blind manner the overall effectiveness of self-administered morphine, meperidine, and oxymorphone in patients recovering from elective cesarean delivery.

Materials and Methods

Following approval by the Human Investigation Committee of Yale University School of Medicine, written informed consent was obtained from 75 patients scheduled for elective cesarean delivery under epidural anesthesia. Patients were free of any significant coexisting disease and had no history of alcohol or drug abuse (ASA PS I or II). Epidural anesthesia was administered *via* catheter using 2% lidocaine with epinephrine 1:200,000 in a volume sufficient to achieve a T4 sensory level.

Solutions of drugs were prepared by the pharmacy so that 1 ml contained either 1.5 mg morphine, 15 mg meperidine, or 0.25 mg oxymorphone. Patients were assigned by a randomization table to receive one of these three agents for postdelivery analgesia. The anesthesiologist and nurse observers remained blinded as to which drug was being administered.

In the Post Anesthesia Care Unit (PACU), when the patient first complained of pain, an analgesic loading dose was given iv in four 1 ml increments 5 min apart. The

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§ Lampert BA, Sundstrom FD, Merrill J, Boyd-Long L: Oxymorphone in PCA. *Anesthesiology Review* 15:35-39, 1988.

TABLE 1. Demographic Data

	Morphine (n = 24)	Meperidine (n = 25)	Oxymorphone (n = 26)
Age (yr)	30.0 ± 1.8	31.0 ± 2.0	31.2 ± 2.6
Height (cm)	159.4 ± 5.7	161.7 ± 4.2	161.1 ± 6.5
Pregnant weight (kg)	79.4 ± 2.4	79.4 ± 2.1	74.1 ± 2.3
Pregnant body surface area (M ²)	2.1 ± 0.1	2.0 ± 0.1	1.9 ± 0.1
Gravida	2.4 ± 0.2	2.5 ± 0.2	2.1 ± 0.2
% Previous cesarean section	75.0	71.4	66.2

Values are mean ± SEM.

dose administered, based on reported potency in this setting,^{6,11,12} was equivalent to 6 mg morphine, 60 mg meperidine, or 1 mg oxymorphone. Additional 1 ml increments of narcotic were titrated iv if the patient requested additional analgesia.

When adequate analgesia had been obtained (*i.e.*, 3–4 cm score on a visual analog scale [VAS] as outlined below) the patient was allowed to self-administer study narcotics as required using a Bard-Harvard PCA Pump® (Bard Medsystems, North Reading, MA) set to administer 1.2 ml boluses (equivalent to 1.8 mg morphine, 18 mg meperidine, or 0.3 mg of oxymorphone) with a lockout interval of 8 min between doses.

After initiating PCA, patients were evaluated for the entire 24-h study interval by one of the four nurse observers specifically trained for this study. Data were collected at first request for pain, following completion of the loading dose, 1, 2, and 4 h following initiation of PCA, and every 4 h thereafter. Each patient was asked to evaluate pain both at rest and at movement using a 10-cm VAS, with a score of 0 cm representing no pain and 10 cm correlating with the worst pain imaginable. Movement scores were taken at 4, 8, 16, and 24 h, 5 min after the patient sat at the bedside and dangled her legs or following brief ambulation. Pain scores thus obtained were graded as mild (VAS 0–3), moderate (VAS 4–6), or severe (VAS 7–10). Patients were asked to use a similar VAS scale to measure their satisfaction with the quality of pain relief provided by the study drug (satisfaction with drug)

TABLE 2. PCA Requirements

	Meperidine	Morphine	Oxymorphone
Total volume administered (ml)	52.9 ± 3.5	57.4 ± 3.7	52.9 ± 2.9
Recovery room volume (ml)	7.5 ± 0.6	7.8 ± 0.5	6.3 ± 0.3
Total volume on ward (ml)	45.4 ± 3.3	49.7 ± 3.1	46.6 ± 2.7
Total mg on ward	681.2 ± 48.8	74.5 ± 4.7	11.7 ± 0.7
mg/h on patient ward	28.3 ± 4.6	3.1 ± 1.1	0.5 ± 0.1
Potency ratio	0.02	0.16	1.00

Values are mean ± SEM.

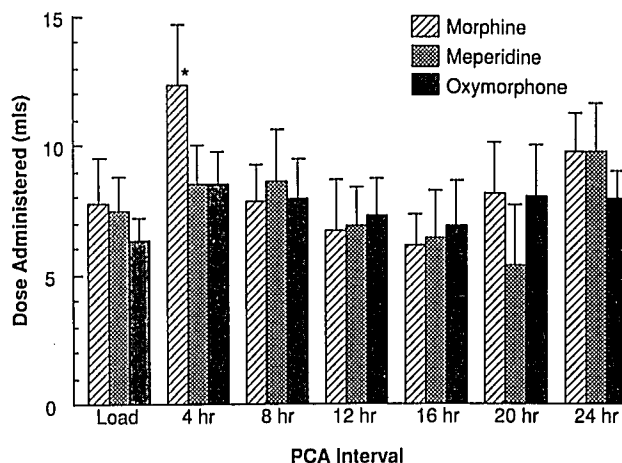


FIG. 1. Mean PCA requirements (ml) over the 24-h study interval for patients self-administering morphine, meperidine, and oxymorphone (error bars reflect SEM). *Significant difference between morphine and both meperidine and oxymorphone ($P < 0.05$).

as well as satisfaction with the concept of controlling their own pain medication with PCA (satisfaction with PCA). A score of 0 cm indicated no satisfaction and a score of 10 cm indicated complete satisfaction. Nurse observers also assessed the patient's level of analgesia using a verbal scale: 0 = no pain, 1 = mildly uncomfortable, 2 = moderately uncomfortable, 3 = very uncomfortable, and 4 = severe pain.

Data collection included the total amount of study drug administered, the number of attempts (demands) by each patient to self-administer study narcotic, the number of injections actually delivered by the PCA pump, and the ratio of injections to attempts (I:A ratio). The apparent level of sedation was assessed in awake patients as follows: 0 = alert, oriented, conversant; 1 = drowsy, oriented, conversant; 2 = drowsy, oriented, nonconversant; and 3 = very drowsy, disoriented, nonconversant. Nausea and vomiting were rated as follows: 0 = none, 1 = occasional mild nausea/vomiting, and 2 = occasional moderate nausea/vomiting. Pruritus was ranked as follows: 0 = none, 1 = mild, and 2 = moderate. Moderate levels of nausea, vomiting, and pruritus were treated in a standard manner with either prochlorperazine (10 mg im) or diphenhydramine (25 mg im) as required. Hydroxyzine (25 mg im) was administered to patients complaining of restlessness and anxiety. The need for treatment and amount of supplemental medication required in each study group was noted.

Data are expressed as percentage or mean ± SEM. Results were analyzed using analysis of covariance with Tukey and paired *t* tests where appropriate. A Pearson *r* correlation was utilized to demonstrate relationships in measured parameters between treatment groups. A *P* value of less than 0.05 was considered significant.

TABLE 3. PCA Attempts versus Injection

	Injections	Attempts	I:A Ratio
Morphine	43.4 ± 2.94	63.0 ± 7.2*	0.69*
Meperidine	37.9 ± 2.8	44.0 ± 4.1	0.86
Oxymorphone	40.0 ± 2.6	49.8 ± 4.6	0.80

Values are mean ± SEM.
* Significant difference between morphine and meperidine, $P < 0.05$.

Results

All patients completed the protocol outlined above without an episode of severe respiratory depression requiring treatment or other significant adverse event. There were no statistical differences between the three treatment groups with regard to demographic variables (table 1), intraoperative anesthetic requirements, and pain scores at the time the analgesic loading dose was administered. The volume of each study narcotic administered in the immediate recovery period and during the 24-h evaluation on the patient ward are listed in table 2. Although total dose requirements were not statistically different, a significantly greater amount of morphine was self-administered during the first 4 h on PCA ($P < 0.05$; fig. 1).

The number of attempts at injection made by patients versus the number of injections actually delivered by the PCA pump is listed for each narcotic in table 3. Initial demands were most frequent in patients in the morphine group, resulting in an I:A ratio that was significantly less ($P < 0.05$) than that observed with meperidine. There was no significant difference in the I:A ratio between the meperidine and oxymorphone treatment groups.

The percentage of patients reporting mild (VAS 0-3), moderate (VAS 4-6), and severe (VAS 7-10) pain at rest throughout the 24-h observation period was found to be similar for patients receiving morphine, meperidine, or oxymorphone (fig. 2). However, when resting pain scores were analyzed in greater detail (fig. 3), the profile of pain intensity as measured at 4-h intervals demonstrated temporal characteristics unique for each narcotic. Pain scores for patients in the morphine group were highest at the early intervals (3.5-4 cm mean VAS) and declined progressively with time, ultimately reaching the lowest level of pain of the three agents studied (1.2 cm mean VAS). A similar delay in peak analgesic effect was observed with meperidine; however, mean pain scores never declined to levels as low as that seen with morphine. Onset of analgesia was most rapid in patients in the oxymorphone group, apparent 15 min following administration of the loading dose, and attaining peak effectiveness 2 h after initiation of PCA. Thereafter, mean pain scores remained uniformly low but never less than 2 cm (VAS). Despite

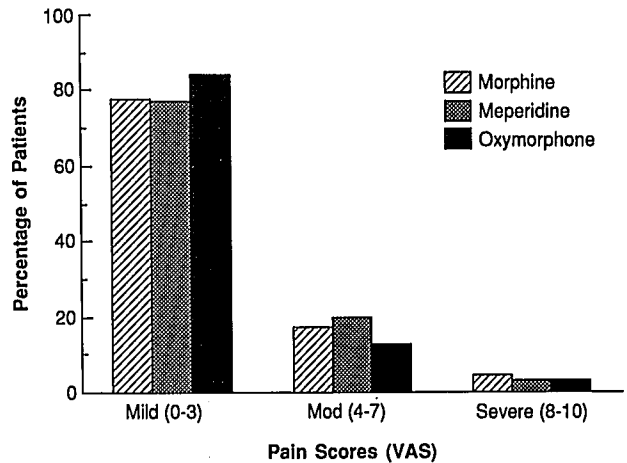


FIG. 2. Percentage of patients self-administering either morphine, meperidine, or oxymorphone via PCA reporting mild (VAS 0-3), moderate (VAS 4-6), and severe (VAS 7-10) pain at rest over the 24-h observation interval.

significant intragroup variability in VAS scores, statistically superior analgesia was noted at 1 and 2 h with oxymorphone and at later intervals (12 and 24 h) with morphine ($P < 0.05$).

The percentage of patients reporting mild, moderate, and severe pain associated with movement over the 24-h study period is presented in figure 4. A greater percentage of patients self-administering meperidine experienced severe pain following a standardized movement stimulus ($P < 0.05$). Mild pain was most often reported in the morphine and oxymorphone groups ($P < 0.05$).

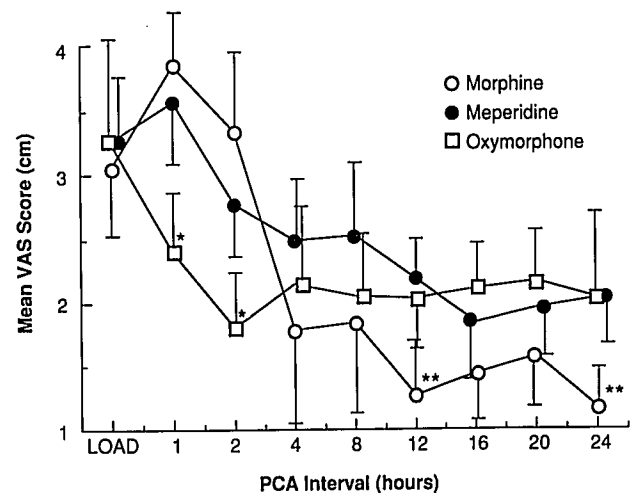


FIG. 3. Mean VAS scores (cm) reflecting pain at rest for patients self-administering morphine, meperidine, and oxymorphone via PCA (error bars reflect SEM). *Significant difference between oxymorphone and both morphine or meperidine ($P < 0.05$); **Significant difference between morphine and meperidine ($P < 0.05$).

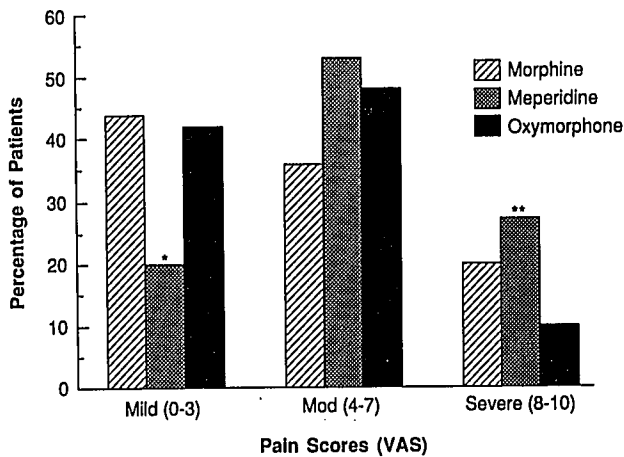


FIG. 4. Percentage of patients self-administering either morphine, meperidine, or oxymorphone via PCA, reporting mild (VAS 0-3), moderate (VAS 4-6), and severe (VAS 7-10) pain on movement over the 24-h observation interval. *Significant difference between meperidine and both morphine and oxymorphone ($P < 0.05$). **Significant difference between meperidine and oxymorphone ($P < 0.05$).

Nurse observer scores, which primarily reflected pain at rest, were unable to detect significant differences in analgesia between treatment groups (morphine 1.58 ± 0.90 , meperidine 1.59 ± 0.83 , and oxymorphone 1.53 ± 0.51), and were consistent with the mild intensity of pain reported with resting VAS scores.

Patient satisfaction and adverse effect scores for each study drug are presented in table 4. Patients treated with morphine had a statistically greater incidence of sedation ($P < 0.05$), a greater percentage requiring treatment for pruritus, and an increased need for hydroxyzine to treat restlessness and anxiety. Patients self-administering oxymorphone had a significantly higher incidence of nausea and vomiting requiring treatment (28%) than did individuals in the morphine and meperidine groups (P

< 0.05). There were no significant differences between groups regarding satisfaction with the concept of PCA or satisfaction with drug when VAS scores were averaged over the 24-h study period. Differences in satisfaction with drug were noted at the 4-h observation interval, however, with scores in the meperidine group significantly higher than those reported for morphine (9.10 ± 0.2 cm vs. 8.11 ± 0.42 cm, respectively, $P < 0.05$). Satisfaction with drug demonstrated negative correlations with resting VAS pain scores (Pearson's $r = 0.509$, $P < 0.01$) and level of sedation (Pearson's $r = 0.488$, $P < 0.05$).

Discussion

The unique characteristics of PCA that allow patients to titrate useful levels of analgesia against tolerable side effects may be best appreciated in individuals recovering from the same surgical stimulus and receiving equianalgesic concentrations of narcotic. The finding that 24-h requirements of the three self-administered study drugs were not significantly different supports the contention that equianalgesic dosing was achieved. Hourly ward requirements of 0.50, 3.1, and 28.3 mg for oxymorphone, morphine, and meperidine, respectively, are in close agreement with potency ratios selected (oxymorphone formulated at six times the potency of morphine and 60 times that of meperidine) and previous recommendations for optimal iv analgesia. In this regard, effective iv analgesia may be achieved with either morphine or meperidine, provided that minimum effective plasma concentrations (MEC) of $21 \mu\text{g/ml}$ and $551 \mu\text{g/ml}$, respectively, or hourly infusion rates of 2.8 mg and 26 mg are maintained.^{6,12} Although the MEC for oxymorphone has not been reported, hourly requirements averaged 0.5-0.6 mg/h when utilized as a PCA analgesic in patients recovering from orthopedic surgery⁸ and cesarean delivery.¹¹

Although mean 24-h narcotic requirements were sim-

TABLE 4. Mean Satisfaction and Side Effect Scores

	Overall Satisfaction with PCA*	Overall Satisfaction with Drug*	Sedation Scale†	% Reporting Moderate Pruritus	% Requiring Treatment Nausea/Vomiting	Supplemental Medication
Meperidine	9.4 ± 0.5	9.5 ± 1.2	0.52 ± 0.44	4.6	9.1	Prochlorperazine (2), Diphenhydramine (1), Hydroxyzine (2)
Morphine	9.3 ± 0.7	8.3 ± 1.3	$1.29 \pm 0.42‡$	9.5	9.5	Prochlorperazine (2), Diphenhydramine (4), Hydroxyzine (4)
Oxymorphone	9.5 ± 0.8	8.9 ± 1.1	0.81 ± 0.47	5.0	28.5§	Prochlorperazine (6), Diphenhydramine (2)

Values are mean \pm SEM. Number of patients treated are given in parentheses.

* Satisfaction VAS scores (cm): 0 = no satisfaction, 10 = complete satisfaction.

† Sedation scale: 0 = alert, oriented, conversant; 1 = drowsy, ori-

ented, conversant; and 3 = very drowsy, disoriented, nonconversant. ‡ Significant difference between morphine and meperidine ($P < 0.05$).

§ Significant difference between oxymorphone and both morphine and meperidine ($P < 0.05$).

ilar, the manner in which patients administered study drugs differed and could be best appreciated by evaluating temporal dosing patterns and injections *versus* attempts (I:A) ratios. In this regard, significantly greater amounts of morphine than either meperidine or oxymorphone were self-administered during the first 4 h on PCA. Analgesic agents having predictable onset, and rapid peak effects are associated with injection *versus* attempt ratios that approach 1.0.¹⁵ Thus, with the concentrations and lockout intervals selected, meperidine offered the best I:A ratio of the three drugs, with oxymorphone second, followed by morphine, which was significantly worse. The lower I:A ratio observed in patients self-administering morphine may reflect its recognized delay in achieving peak analgesic effect.^{2,12} This latency has been attributed to the blood-brain barrier, which slows CNS penetration of this hydrophilic alkaloid following parenteral administration.

Relatively large individual differences in narcotic consumption were present in each of the treatment groups. Such variations could not be attributed to differences in patient age, weight, body surface area, or prior history of cesarean delivery. This absence of correlation between weight and narcotic dosage required for subjective analgesia is in agreement with previous PCA evaluations.^{12,13} Despite the variability in dose requirements and significant pharmacokinetic differences among study drugs,^{6,8,12} all three agents provided excellent pain relief. Although there was no statistical difference in resting pain scores over the 24-h study interval, the patterns by which patients attained optimal levels of analgesia were dissimilar. Morphine characteristically had the slowest onset of relief, although pain intensity declined steadily after 4 h. This latency suggested that morphine, as self-administered in the present investigation, had difficulty attenuating the intense pain stimulus that followed resolution of epidural anesthesia in patients receiving no premedication and minimal intraoperative analgesics. Delays in morphine's peak analgesic effect could conceivably be reduced by administering earlier and/or larger loading doses or by decreasing the lockout interval duration during the first few hours on PCA; such changes in dosing, however, might be expected to further increase patient sedation and the incidence of adverse effects.

A slow onset of resting analgesia that improved steadily during the first 16 h was also noted in patients self-administering meperidine. Meperidine was least effective, however, in controlling pain associated with patient movement. This finding confirms a similar inability to blunt movement-associated pain noted in a prior PCA comparison of meperidine and nalbuphine.¹⁴ Factors responsible for this lack of efficacy remain unclear but may be related to the fact that meperidine has a low receptor

affinity and a relatively short duration of peak effect.^{6,13,14} Thus, if patients who were comfortable at rest did not anticipate movement by injecting additional drug, the sudden increase in pain stimulus might not be successfully attenuated.

Patients self-administering oxymorphone achieved rapid analgesic onset and little variability in rest and movement pain scores. Since onset and potency of opioid analgesia may be related in part to CNS accessibility,¹⁵ the high lipid solubility¹⁶ and binding affinity¹⁷ of oxymorphone may permit rapid CNS penetration and activation of opiate receptors. Oxymorphone's analgesic pattern represented a compromise in that patients were spared excessive discomfort during the early postdelivery hours, although they were unable to achieve the degree of pain relief observed at later intervals with morphine. It is conceivable that patients self-administering oxymorphone tolerated higher pain scores knowing that, if desired, they could rapidly obtain additional analgesia.^{11,§} An alternative explanation recognizes the fact that patients utilizing PCA may consciously or unconsciously trade off between effective (but less than total) analgesia and increases in adverse effects.^{1,4,18} The significantly higher incidence of nausea noted in the oxymorphone group, which was not recognized in two prior PCA evaluations,^{11,§} supported this contention.

Satisfaction with drug effect demonstrated an inverse relationship with resting pain scores and was lowest initially in the morphine group. Factors responsible for reduced patient satisfaction with morphine may include early delays in peak analgesic effect, higher levels of sedation, and a greater need for supplemental medication. In this regard, it was unclear why patients self-administering morphine had the greatest need for hydroxyzine and whether such therapy influenced the level of sedation, pain scores, and incidence of nausea. Nevertheless, the observed negative correlation between level of sedation and satisfaction indicates the importance of low sedation scores in postdelivery patients. The finding that overall patient satisfaction with drug effect correlated with resting but not movement pain scores may be related to the relative infrequency of ambulation attempts or the high variability/decreased sensitivity of quantitative VAS assessments. Recent investigations evaluating self-administered analgesics have suggested that the complex nature of postoperative pain may be further assessed by evaluating qualitative, emotional, and affective components.^{18,19}

In conclusion, three narcotic analgesics self-administered in equianalgesic concentrations provided effective postoperative analgesia with high patient satisfaction and few adverse effects. Although morphine is a more commonly utilized drug for PCA, the excellent quality of an-

algnesia, low incidence of sedation, and high degree of patient satisfaction provided by meperidine and oxymorphone suggest two useful alternatives.

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