Combination of nerve blockade and intravenous alfentanil is better than single treatment in relieving postoperative pain

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Background/Purpose: Multimodal analgesia can improve perioperative analgesia but knowledge of combination protocols is still incomplete. This study was designed to evaluate whether the combination of sciatic nerve blockade (SNB) and intravenous alfentanil (IVA) is more effective than either single treatment in relieving postoperative pain in rats.

Methods: In a plantar incision model, withdrawal thresholds were evaluated by von Frey test before incision as baselines and for 7 days after incision. The animals were randomly allocated into various groups to receive SNB with 1% or 2% lidocaine, IVA of 50 or 150 μg/kg, or combined treatments (SNB 1% + 50 μg/kg IVA or SNB 2% + 150 μg/kg IVA) before incision. The results were compared with those of sham procedures—i.e., injections of peri-sciatic or intravenous saline, or a combination of both.

Results: Plantar incision caused postoperative allodynia for 3 days. SNB with 2% lidocaine reduced allodynia at 1 hour, 3 hours, day 1, and day 2, but not at postoperative 5 hours or days...
Introduction

Surgical pain is a common predictable pain in hospitals. Ineffective pain control decreases patient satisfaction, delays hospital discharge, increases morbidity,1,2 and even leads to chronic postsurgical pain syndrome.3 For better pain control, multimodal analgesic techniques through different inhibitory pathways at the perioperative period were suggested by studies4 and by the Guidelines for Acute Pain Management by ASA Task Force.5 Nevertheless, the Guideline did not recommend any optimal combination protocols. Although single or multiple analgesic techniques have all been widely investigated,6 it is still difficult to predict their actions on a distinct pain quality because the mostly used pain measurement in clinical studies, such as visual analog scale, can only reflect generalized pain perception rather than a distinct pathological reaction.

Therefore, we examined the efficacy of two mechanism-independent modes of analgesic techniques i.e., sciatic nerve blockade (SNB) and intravenous opioid, administered separately or in combination, on reduction of mechanical pain in a rat plantar incision (PI) model. Postoperative mechanical hypersensitivity is a common problem directly interfering with postsurgical movements, wound dressing changes, and daily rehabilitation. Mechanical allodynia is an objective sign indicating a specific nociceptive sensitization in a prolonged pathological process after tissue injury, and can be quantitatively measured by tactile-responsive tests. This sign can be more easily accessed in animals than in humans, because infection at surgical wound is less concerned. Meanwhile, lidocaine, a popular local anesthetic with a pharmacologically short action, and alfentanil, a pure μ-receptor agonist similar to fentanyl but with a much shorter effect, are selected, because the surgical period is short in this study (about 5 minutes). We intentionally included the two agents to test our hypothesis—whether combining two efficacious but short-acting i.e., only intraoperatively effective, anesthetic/analgesic techniques could result in a prolonged, synergistic postoperative analgesia.

Materials and methods

Subjects

Male Sprague–Dawley rats (250–300 g; BioLASCO Co., Taipei, Taiwan) were housed in groups of three to four in a temperature- (23 ± 1°C) and humidity- (50% relative humidity) controlled animal room with a 12-h light/dark cycle. Food and water were provided ad libitum. The experiments were approved by the Animal Care and Use Committee of Shin-Kong Wu Ho-Su Memorial Hospital and strictly followed the ethical guidelines issued by the International Association for the Study of Pain.7 Efforts were made to minimize the number of rats used.

Plantar incision pain model

This model was previously reported,8,9 and had been proven to reliably mimic human postoperative pain with several lines of evidence.8,10,11 In brief, the plantar surface of the left hind paw was longitudinally incised for 1 cm under 2% isoflurane anesthesia. The plantaris muscle was incised, leaving the origin and insertion intact. After skin suture, the rats were moved to an elevated mesh for behavioral testing. During the experiments, rats with wound infection were excluded.

Behavioral responses to von Frey stimulation

Postoperative mechanical pain was evaluated by von Frey test. Two or 3 days before PI, rats were placed in a chamber (10 × 10 × 20 cm) of Plexiglas boxes on an elevated metal mesh for at least 30 minutes and stimulated by von Frey fibers for habituation. The von Frey stimulation was applied from the mesh opening to the plantar surface near the medial heel using the up–down method,12 with a series of von Frey fibers (0.4, 0.6, 1, 2, 4, 6, 8, and 15 g; Stoelting, Wood Dale, IL) starting from a 2-g fiber. The 50% threshold at each time point was calculated and averaged from two measurements, separated by 5 minutes.9 The time points included a baseline obtained 1 hour before surgery and at postoperative 1 hour, 3 hours, 5 hours, 1 day, 2 days, 3 days, 5 days, and 7 days. The experimenter for the behavioral testing had no knowledge of the rat allocation.

Experimental design and analgesic techniques

The analgesic effects of SNB with 1% or 2% lidocaine (Lido) or intravenous alfentanil (IVA; 50 or 150 μg/kg) were first evaluated separately, then we examined the efficacy of combining the two techniques in low-dose (SNB 1% Lido + IVA 50 μg/kg) and high-dose (SNB 2% Lido + IVA 150 μg/kg) combinations. To avoid confounding the effects of surgical and injection procedures, the control groups and single-treatment groups in all experiments received
adequate sham procedures for comparison. There were three different sham procedures: peri-sciatic saline injection, intravenous saline injection, or their combination. Therefore, seven groups were derived, and rats were allocated to different treatments (Fig. 1); (1) SNB1: SNB with 1% lidocaine followed by intravenous saline injection (i.e., a sham IVA); (2) SNB2: SNB with 2% lidocaine and then sham IVA; (3) IVA50: sham SNB first, then followed by IVA (50 µg/kg); (4) IVA150: sham SNB followed by IVA (150 µg/kg); (5) SNB1 + IVA50: SNB with 1% lidocaine followed by IVA (50 µg/kg); i.e., a low-dose combination; (6) SNB2 + IVA150: SNB with 2% lidocaine then IVA (150 µg/kg; i.e., a high-dose combination); (7) control sham group: sham SNB followed by sham IVA. We always started with SNB because it took a longer time to take effect. IVA was administered next and took about 20 minutes, including needle insertion and drug infusion. All treatments were conducted under anesthesia and before PI (see Fig. 1).

Sciatic nerve blockade

The sciatic nerve was exposed via incision of the left lateral thigh and division of the superficial fascia and muscle as previously described.13 With a 30-G needle tuberculin syringe, a total 100 µl of 1%, 2% lidocaine, or saline was injected beneath the fascia at both sides of the nerve. The injectate formed a clear bulb surrounding and outside the perineurium without breaching it. The muscles were sutured by layers, and the wound was closed with 3–0 silk.

To avoid mistaking the SNB-induced motor blockades as an analgesic effect, the neurobehavioral tests were conducted in a separate group of naive rats without PI. For motor testing, the force of the extensor postural thrust in the injected hind limb was evaluated as previously described.13 The rat was held upright with the hind limbs extended so that the toes supported its weight. The reduction of the thrust force was estimated by the preserved force and was converted to a score (0: baseline or no block; 1: minimal block, force within 50–100% of preinjection value; 2: moderate block, force below 50% of the preinjection value but not flaccid; 3: complete block, flaccid, and no thrust power). Meanwhile, sensory blockade was evaluated using withdrawal reflex or vocalization in response to a pinch of the distal phalanx of the fifth toe.

The reactions were graded on a scale (0: normal, brisk withdrawal reflex or escape behavior, and strong vocalization; 1: mildly impaired; 2: moderately impaired; and 3: totally no nociceptive reaction).

Additionally, systemic lidocaine was reported to produce an analgesic effect on incision-induced secondary allodynia.14 To rule out this possibility, another group of rats received intramuscular injection with 0.5 ml of 2% lidocaine in the right-side back muscles as a positive control. PI was conducted 30 minutes after injections.

Intravenous alfentanil

Alfentanil hydrochloride (Rapifen®; Janssen-Cilag, Beerse, Belgium) or saline vehicle was given into the tail vein via an inserted 30-G needle. Successful cannulation was ensured by free backflow with blood. Alfentanil of two concentrations (50 or 150 µg/ml) was infused at a rate of 25 µl/minute, using a syringe pump (Model KDS 210; KD Scientific Inc., New Hope, PA, USA) to final doses of 50 or 150 µg/kg, respectively, in about 10–12 minutes. This dose was based on a previous study of single dose alfentanil on formalin-induced pain.15 Rats with incomplete injections were excluded.

Statistical analysis

Data were expressed as means ± standard error of the means (SEM). Post-incision threshold changes were compared with their baseline data (Pre) using repeated-measures analysis of variance. Analgesic effects among the groups at each time point were compared by one-way analysis of variance followed by post hoc Bonferroni’s test. The neurobehavioral blockade scores of SNB test in naive rats are ordinal data and were expressed as medians with first and third quartiles for nonparametric analysis. The blockade effects over time were compared using Friedman’s test. A value of p < 0.05 was considered statistically significant. At least nine rats were included in each group.

Results

PI resulted in mechanical allodynia

Incision at plantar surface of the hind paw resulted in noxious responses to von Frey filament stimulation as shown in the results of the control group in the present study and previous reports.8,11 Withdrawal thresholds decreased immediately and lasted for 3 days after surgery (the control sham group in Figs. 2–5), indicating a persistent nociceptive hypersensitivity induced by PI. On the fifth postoperative day, mechanical responses to von Frey fibers returned to preoperative levels.

S NB produced a moderate but prolonged analgesic effect

Nerve block pretreatment with 1% lidocaine mildly reduced postoperative allodynia (not statistically significant), whereas SNB of 2% lidocaine efficaciously suppressed incision-induced allodynia for about 2 days, with statistical
significance for the first 3 hours and at 1 and 2 days after surgery (Fig. 2). The withdrawal thresholds were increased from 1.22 \pm 0.25 to 4.94 \pm 1.25 g at 1 hour and from 2.54 \pm 0.40 to 5.27 \pm 0.96 g at 3 hours (control vs. SNB2, both \( p < 0.01 \)). The early antiallodynic effect was moderate compared with the strong effect of IVA (as shown below). The 2\% SNB, 1\% SNB, and control groups clearly exhibited a dose-dependent relationship. No statistical difference in the preoperative baseline thresholds was found among the groups.

Figure 2: Effects of sciatic nerve blockade (SNB). Before PI, rats were subjected to either SNB with 2\% or 1\% lidocaine followed by intravenous saline infusion (i.e., SNB2 and SNB1). The control rats received sham blockade with saline and IV saline (i.e., Cont, Sham). PI produced a significant decrease of thresholds in the control group (\( n = 9 \)) for postoperative 3 days. SNB1 (\( n = 8 \)) did not significantly alleviate mechanical allodynia, whereas SNB2 (\( n = 10 \)) significantly inhibited pain at 1 h, 3 h, 1 d, and 2 d after surgery compared to the control. Repeated-measures analysis of variance (ANOVA) with post hoc Bonferroni’s test, \#p < 0.05, \#\#p < 0.01 vs. pre-op baseline (Pre); one-way ANOVA with post hoc Bonferroni’s test, \(*p < 0.05\), \**p < 0.01 vs. control. No difference was found between SNB2 and SNB1 at any time point.

Figure 3: Effects of intravenous alfentanil (IVA). Rats were subjected to either IVA with 150 or 50 mg/kg alfentanil infusion from tail vein after peri-sciatic injection with saline (i.e., IVA150 and IVA50). The control rats received sham blockade and sham injection as shown in the Fig. 2 (i.e., Cont, Sham). IVA50 (\( n = 9 \)) had significantly mild antiallodynic effect for 3 h and IVA150 (\( n = 9 \)) produced stronger inhibition at the same period compared to the control and the IVA50 group. One-way ANOVA with post hoc Bonferroni’s test, \(*p < 0.05\) and \**p < 0.001 for IVA50 and IVA150 vs. control; \++p < 0.01 and +++p < 0.001 for IVA150 vs. IVA 50.

Figure 4: Effects of combination of sciatic blockade and intravenous alfentanil. Rats were subjected to either low-dose combination (SNB1 followed by IVA50, or SNB1 + IVA50) or high-dose combination (SNB2 + IVA150) before PI. The control rats received sham blockade and sham injection as shown in Fig. 2 (i.e., Cont, Sham). The low-dose combination (\( n = 8 \)) was surprisingly not efficacious when compared with the control group, whereas the high-dose combination (\( n = 8 \)) produced a long and strong suppression on postoperative allodynia compared to the low-dose combination and the sham group at postoperative 1 h, 3 h, 1 d, and 2 d. One-way ANOVA with post hoc Bonferroni’s test, \(*p < 0.05\) and \***p < 0.001 for SNB2+IVA150 vs. control; \++p < 0.01 and +++p < 0.001 for SNB2+IVA150 vs. SNB1+IVA 50. No difference was shown between low-dose combination and the control.

Figure 5: A comparison of analgesic effect between the high-dose combination treatment and two high-dose single treatments. All data are the same as lines in Figs. 2, 3, and 4. Notably, high-dose combination of SNB and IVA produced a strong antiallodynic effect over any single treatment and sham treatment at the early postoperative period (1 and 3 hours); however, the combination did not produce a stronger effect than any single treatment at the delayed period (1 and 2 d). No synergistic effect of multimodal treatment on postincisional allodynia was observed in this treatment profile. One-way ANOVA with post hoc Bonferroni’s test, \(*p < 0.05\), \**p < 0.01, and \***p < 0.001 for groups vs. control; \+p < 0.05 and +++p < 0.001 for SNB2+IVA150 vs. SNB2.
IVA produced a strong but short analgesia after surgery

IVA showed an analgesic pattern different from SNB (Fig. 3). Both the low-dose (IVA 50 µg/kg) and high-dose (IVA 150 µg/kg) groups induced a significant reduction in postoperative allosthenia; however, these effects were not sustained after 5 hours. The high-dose group produced a much stronger antiallodynia for the first 3 hours compared to the low-dose and control groups. Dose-dependent effects were observed at 1 and 3 hours. Although after 1 day the alfentanil-treated groups still had mildly analgesic effect compared to the control group, it did not reach statistical significance.

It was also observed that high-dose alfentanil caused transient trunk rigidity and sigh respiration within the first 3–5 minutes after the start of infusion, and a slightly longer recovery time in the high-dose group; however, all rats recovered well within 20 minutes after the end of PI.

Combination of SNB and IVA produced a strong, long-lasting analgesic effect

When SNB and IVA were administered together, a combined analgesia was observed (Fig. 4). The high-dose combination (SNB2 + IVA150) significantly reversed the postoperative allosthenia at 1 hour, 3 hours, 1 day, and 2 days after incision when compared with the low-dose combination group (SNB1 + IVA50) and the sham control group. Surprisingly, the low dose combination did not produce any analgesic effect when compared with the sham group, indicating that no additive or synergistic effect occurred. To compare the multimodal combination with the single combination, their effects were plotted in the same diagram (Fig. 5). Clearly, the analgesic effect of the high-dose combination was strong and long-lasting, but apparently not a synergism of both single treatments. During the early (1–3 hours) postoperative period, the combination effect was seemingly addictive; and during the late period (1–2 days), the combination did not differ much from the SB2N group. Altogether, our data demonstrated that the combination of SNB and IVA treatments was able to improve post-PI allosthenia mildly or moderately compared to any single treatment with SNB or IVA.

Lidocaine block did not affect behavioral evaluations or yield systemic analgesia

The motor and sensory blockades by 2% SNB were examined in this study (Fig. 6A). SNB completely abolished the thrust force of the left hind foot and nociceptive reflex to a pinch at the toe. The recovery of both functions was paralleled along time, and a full recovery (i.e., to a level of no statistical difference) in sensory and motor tests occurred respectively at 60 and 70 minutes after blockade, indicating that the SNB in this study did not directly interfere with muscle power in response to von Frey tests conducted at 1.5 hours later (i.e., 30 minutes before plus 1 hour after PI). In another study, an intramuscular lidocaine injection did not alter the post-PI withdrawal hypersensitivity (Fig. 6B), demonstrating that systemic absorbed lidocaine had little

![Figure 6](image-url) In naı̈ve rats, SNB of 2% lidocaine (n = 5) elicited parallel motor and sensory blockade [upper and lower panels in (A)]. (A) The neurobehavioral functions recovered to the pre-injection level 70 min later, indicating a short-term effect of SNB. Solid and dotted lines in each box respectively stand for median and mean values. Data were compared by Friedman’s test, \#p < 0.05 and \#\#p < 0.01 vs. baseline data (time point: Pre-SNB). (B) Effect of the intramuscular lidocaine (2%, 0.5 ml) injection at the back muscles (IM2). No significant difference was found between the control group (control, Sham, n = 9) and the IML group, suggesting that systemic absorption of lidocaine has no antiallodynic effect at post-PI period.
contribution to postoperative allodynia and that the SNB-induced analgesia is mostly a result of conduction blockade.

Discussion

The present study showed that, in a rat incision model, pretreatment with SNB of 2% lidocaine produced moderate and prolonged antiallodynic effect for 2 days after surgery, whereas IVA of 150 μg/kg strongly reduced postincisional allodynia for only 3 hours. A combination of these two treatment modes led to a remarkable improvement in analgesic efficacy, although no long-duration effect was observed. Notably, no synergistic analgesia was observed when the two treatments were combined at lower doses.

In the clinical setting, multiple analgesic/anesthetic techniques were coadministered as a “balanced anesthesia” to obtain a better aesthetic quality and to reduce intra- and postoperative pain.5,16 Because pain is a dynamic process involving multiple sensitizing processes,17 wide variations in types of surgery, personal sensitivity to pain, psychocognitive differences, and individual pharmacological responses altogether confound the ultimate analgesic efficacy. Different degrees of success were shown among studies even though the combination protocols were the same. Moreover, postoperative patient-controlled analgesia with morphine has been recognized to be problematic in terms of tolerance, dependence, and opioid-induced hyperalgesia.18 As a result, clinical investigators have begun to examine the additional benefits of combining nonopioid analgesics or conduction blockades with local anesthesia, regional blocks, or spinal anesthesia.6 With the increasing popularity of ultrasound-guided techniques, nerve blocks have become safe and are widely used as routine anesthetic approaches,19,20 especially for lower limb surgery.20,21 Because there is no formulated protocol to suggest any standardized combination for individual surgical pain, our findings from a PI model in rats can directly generate informative and comprehensive implications to clinical studies.

A particular finding in this study is that the short-duration SNB produced a long-lasting after-effect on postincisional allodynia. In the 2% lidocaine group, SNB first suppressed immediate postoperative pain for 3 hours and sustained the antiallodynic effect for 2 days. Our finding is compatible with many clinical experiences in that regional anesthesia attenuated postoperative pain far outlasting the anesthetic duration. It is generally accepted that conduction anesthesia, in addition to its temporal blockade of intraoperative nociceptive impulses to dorsal root ganglia, also preempts the activation of spinal N-methyl-D-aspartate receptors and inhibits the development of central sensitization.4,17 Therefore, a short-acting agent can produce acute analgesia by itself, and prolonged effect through sustained inhibition on neuronal hypersensitivity. This biphasic effect has been shown with evidence of Fos expression in neuropathic pain and allodynic behaviors in a back incision pain model.14,22

Beyond behavioral observations, various molecular changes may underlie the sensitizations. In our study as well as in other previous studies, microglial activation is found to be involved in incisional pain development,9,23—25 and p38 activation in spinal microglia plays a key role in the regulation of important nociceptive downstream signaling processes.9,23,26 We found that pretreatment with p38 inhibitor effectively prevented post-PI mechanical allodynia; however, preemptive nerve blockade with bupivacaine could only prevent, but not reverse, spinal p38 phosphorylation and nerve injury-induced hypersensitivity.27 Because phosphorylation of p38 (p-p38) within microglia has been suggested as a hallmark of the development process in central nociceptive sensitization,9 it is rational to assume that pretreatment with short-acting SNB could preemptively inhibit p-p38 induction by surgery to facilitate the antiallodynic effect for 2 days. A more recent study further suggested a long-lasting analgesic effect by lidocaine through attenuation of proinflammatory cytokine production.28 Nevertheless, this inhibitory effect of lidocaine may have been too weak in this study since no analgesia was observed via intra muscular lidocaine injection.

In light of the above-mentioned complexities, it is not surprising that contradictory results were reported. Wound infiltration with 1% bupivacaine in Pogatzki et al’s study29 or SNB with 0.5% bupivacaine in Ririe et al’s study30 was not able to reduce postincisional allodynia longer than 3 hours. Both of these studies might be less effective compared to the present study in that first, the local infiltration used by Pogatzki et al is not the same as the nerve blockade used in this study, and second, the block technique in Ririe et al’s study is a blind injection. Taken together, an important implication from these studies is that although transmission blockade can prevent incision-induced allodynia, its effectiveness may critically depend on minor differences in pain origins, blockade time, and blockade quality. Other factors can also influence the SNB efficacy. For example, first, transmission blockade cannot completely impede spinal neurons from reactions to all afferent impulses. Lidocaine cannot sufficiently block action potentials in all types of sensory fibers (myelinated Aβ, Aδ, and unmyelinated C fibers), and spontaneous ectopic firing can still be generated proximal to the blockade site.31 Second, the medial aspect of the plantar paw near the heel, the area where von Frey fibers are stimulated, is innervated by the tibial nerve, a branch of the sciatic nerve. However, the border adjacent to the medial foot is also innervated by the saphenous nerve, a branch of the femoral nerve. It is possible that SNB did not abolish the transmission through the saphenous nerve and thus the incision-induced peripheral sensitization at saphenous nerve could escape the effect of 2% SNB. These two reasons may explain the low efficacy of SNB at the early postoperative period.

In this study, the short-acting alfentanil induced a reliable and dose-dependent peri-operative analgesia for 3 hours; however, increasing the dose did not produce a prolonged effect over 1 day. In short, no preemptive effect was observed. Such result is not surprising because opioid-induced long-term analgesia has been questioned, especially when high-potent or high-dose opioids are used. For example, morphine and D-Ala2-NMe-Phe4-Glyol5-enkephalin strongly attenuated the formalin-induced spinal Fos expression or neuronal firing spikes at the second phase of hyperalgesia when given before, but not after, formalin
In contrast, high doses of alfentanil or morphine were reported to have no late-phase analgesia in the same protocol. Moreover, acute tolerance and opioid-induced hypersensitivity may occur after a rapid alfentanil administration by activating postsynaptic N-methyl-D-aspartate receptors and attenuating their long-term effect. Furthermore, a growing body of evidence has proved that microglia possess opioid receptors. Chronic morphine administration can activate spinal microglia to increase intracellular p-p38 and to antagonize the original morphine analgesia via the simultaneous releases of proinflammatory mediators. It is thus presumed that SNB before PI could inhibit microglial p-p38 to prolong antiallodynia, whereas IVA might sensitize the spinal glial system to counteract the production of long-lasting analgesia. Taken together, these theories can explain, at least partially, why IVA has such a good, short analgesia, and why IVA and SNB combination did not exhibit an expected strong-and-long analgesia.

In this study, the combination of IVA and SNB showed an additive-like analgesic effect from the individual action of two single treatments, especially at the first 3 postoperative hours. Disappointingly, there was no evidence indicating that an additive or synergistic effect was produced by the combination treatment during the delayed period (days 1 and 2 in this study). Usually, isobolographic analysis is used to confirm pharmacological addition or synergism, but it is impossible to perform this analysis for lack of sufficient dose-dependent data. However, the combination treatment used in the current study is clearly not a synergism because, first, the low-dose combination did not produce a significant analgesia, and second, instead of showing a stronger effect, the high-dose combination group contrarily displayed weaker effects at 1 day and 2 days compared to those of the SNB group.

Although no synergistic effect is observed in this study, we cannot exclude the possibilities that it may happen in other pain models (such as inflammatory pain or different surgical pains), pain characters (spontaneous pain or thermal pain), or analgesic combinations (such as opioid plus spinal block). Accordingly, we suggest that, first, a combination of two or more effective treatments does not guarantee synergistic effects on all kinds of pain perception; second, multimodal analgesia for postoperative pain should be carefully judged and formulated; and third, intraoperative neural blockade may be more important than intraoperative opioids for the optimal control of persistent postoperative pain hypersensitivity. A vast number of preclinical studies to clarify the individual efficacies and mechanistic interactions among distinct combinations are still required to avoid too much waste of medical resources through empirical trials.

In conclusion, this study demonstrated that pretreatment with multimodal analgesia is superior to single or no pretreatment in attenuating postoperative allodynia. It is also suggested that coadministration of mechanism-independent protocols may interactively act on nociceptive cascades to generate synergistic or even antagonizing effects. More clinical and mechanistic investigations are necessary to determine the optimal combination protocols for a better postoperative pain management.

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