To compare the efficacy of propofol with ketamine versus propofol with fentanyl for procedural sedation for patients undergoing endoscopic retrograde cholangiopancreatography

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Abstract

Objective: This study was conducted to compare the efficacy of Propofol with Ketamine versus Propofol with Fentanyl for procedural sedation for patients undergoing ERCP to evaluate Propofol consumption, recovery score, patient satisfaction and sedation related adverse events.

Materials and Methods: Sixty patients aged 18-60 years, ASA Class I and II were randomly allocated to one of two groups; Propofol/Ketamine (Ketofol) group KP (n=30) and Propofol/Fentanyl group FP (n=30). The level of sedation was adjusted to achieve a Ramsay Sedation Scale (RSS) score of 5.

Results: The total amount of Propofol consumed was significantly higher in FP group (109.88±11.3871 mg) compared to KP group (89.867±9.8942 mg). Time to reach acceptable recovery score was slightly longer in KP group compared to FP. Patient satisfaction was comparable in both the groups and sedation related side effects like hypotension, bradycardia, desaturation was more significant in FP group compared to KP group.

Conclusion: Propofol-Ketamine combination provided sedation quality similar to Propofol-Fentanyl combination with better hemodynamic profile and fewer side effects. Hence Propofol-Ketamine combination can be safely used in patients undergoing ERCP.

Keywords: Propofol, ketamine, fentanyl, sedation score, recovery score, patient satisfaction, side effects

Introduction

Procedural Sedation and Analgesia, previously known as conscious sedation, is defined as a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function. According to the American Society of Anesthesiologists (ASA), sedation is defined as a continuum of progressive impairment in consciousness ranging from minimal to moderate, deep sedation and general anesthesia[1].

In mild sedation, patient responds normally to verbal stimulus, airway is maintained, ventilation is adequate and cardiovascular function is unaffected. In moderate sedation, patient has purposeful response to verbal or tactile stimulus, ventilation is adequate, cardiovascular function is usually maintained and airway intervention is not required. In deep sedation, patient has purposeful response to repeated or tactile stimulus, cardiovascular function is usually maintained, ventilation may be inadequate and airway intervention may be needed. In general anesthesia, patient is unarousable even to painful stimulus, ventilation is frequently inadequate, cardiovascular function may be impaired and airway intervention is often required. The goals of sedation are to achieve a balance between the benefits of sedation against potentially preventable risks. Sedation reduces pain, discomfort and stress and can produce amnesia in patients undergoing unpleasant and prolonged procedures.

ERCP is a routinely carried out diagnostic and/or therapeutic procedure for the biliary tract and pancreas, which is done by endoscopy after injecting contrast dye through the duodenal papilla. Certain painful procedures may also be performed during ERCP such as stenting, stone removal, visualization of the pancreaticobiliary tract, laser lithotripsy and sphincterotomy [2-5] in various clinical conditions. It is an uncomfortable, distressing and painful procedure carried out in prone or semi prone position.
These patients require sedation mainly to minimize their anxiety and analgescs to alleviate pain and discomfort. This enhances patient’s cooperation throughout the procedure. The main challenges for the anesthesiologist during ERCP are apnoea and airway obstruction, particularly with the patient in the prone position (due to the unavailability of the airway) [3, 4, 6, 7].

A variety of drugs have been used. Available agents for sedation include benzodiazepines (Midazolam, Diazepam), narcotics (Fentanyl, Meperidine), Propofol, neuroleptic tranquillizers (Droperidol), antihistamines (Diphenhydramine) and dopaminergic receptor antagonists (Promethazine) [8, 9]. Ketamine etc. Traditionally Propofol has been used in combination with Fentanyl to attain adequate levels of sedation and analgesia compatible with the procedure. Propofol with rapid recovery profile produces sedation and amnesia and has been increasingly used worldwide as a sedative agent for standard endoscopy [10-16]. But it has been observed that Propofol is associated with complications such as hypotension, respiratory depression, arterial oxygen desaturation, bradycardia, nausea and vomiting [2, 17, 19] when used in combination with Fentanyl. Midazolam, a benzodiazepine commonly used in sedation, has sedative, amnesic and anti-anxiety effects but no analgesic effect [2, 20]. It is used commonly in combination with opioids for sedation. Fentanyl, a short-acting opioid, is useful for upper gastrointestinal endoscopic procedures and produces analgesia and sedation [21, 22]. According to Thomson A, et al. Fentanyl with Midazolam produces shorter recovery time as compared to Meperidine with Midazolam without any difference in pain perception [8]. Remifentanyl is another short-acting opioid that is available for sedation and produces intense analgesia with minimal residual effect. Ketamine, a synthetic phencyclidine derivative, has been pronounced as a safe and effective sedative agent. Ketamine produces a dissociative state, combination of analgesia, amnesia and sedation at sub-anesthetic dose with minimal effects on the airway and vital reflexes. As Ketamine does not cause respiratory depression and maintains spontaneous ventilation, we used Ketamine with Propofol in our study, assuming Ketamine and Propofol combination would provide deep sedation, stable hemodynamics, lesser post-operative nausea and vomiting with shorter discharge time [19, 23, 26]. Hence the present study was conducted with the aim to compare the efficacy of Propofol with Ketamine versus Propofol with Fentanyl for procedural sedation for patients undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP).

Materials and Methods
A prospective, randomized, double blinded study comparing the efficacy of Propofol with Ketamine Versus Propofol with Fentanyl for procedural sedation for 60 patients, aged 18-60 years, undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP).

Inclusion Criteria
- Patients consented for study
- Patients aged between 18 to 60 years
- Patients of either sex
- Patients of ASA Grade I and II

Exclusion Criteria
- Patients not consented for study
- Patients with history of cardiovascular disease, bradycardia, ischemic heart disease, uncontrolled hypertension, diabetes mellitus and renal dysfunction
- Patients having known allergy to the study drugs
- Patients of ASA Grade III, IV and V
- Emergency ERCPs
- Bleeding or coagulation abnormalities
- Patients unable to cooperate with dementia, psychosis etc.
- Pregnants

Study groups
Study population was divided into two groups.
- Group 1: Propofol and Ketamine (KP)
- Group 2: Propofol and Fentanyl (FP)

Randomization: A computer-generated table of random numbers was prepared allotting equal number of patients in each group.

Place of study: Bhaskar Medical College, Moinabad, Hyderabad.

Duration of the study: December 2021 to August 2022

Blinding: Pre-operatively patients meeting the inclusion criteria for the trial were allotted a serial number and case record forms with the allotted serial number mentioned on them. Drugs KP or FP as per the randomized chart were injected by one of the investigators. Neither patients nor observer were told about the drugs injected. Decoding of serial numbers and drugs received by the patient were done at the end of study.

Sample size: The number of participants required in each intervention group—n was calculated by:

\[ n = \frac{2\sigma_p^2(z_{1-\alpha/2} + z_{1-\beta})^2}{\mu_d^2} \]

\[ S_p^2 = \frac{S_1^2 + S_2^2}{2} \]

We have taken the following data for recovery time from the previous article, Hasanein R, El-Sayed W, et al. [3], to compare two techniques of sedation for obese patients undergoing ERCP, using either Propofol-Ketamine or Propofol-Fentanyl.
- Recovery time recorded for Propofol-Ketamine: 11.19±2.59 min
- Recovery time recorded for Propofol-Fentanyl group: 9.43±1.23 min Based on the above values, considering the effect size is 0.92, assuming the power is 90% and alpha error is 5% with two sided, the sample size for each group was calculated as 30. Total sample size = 2 ×30 = 60

The following parameters were monitored for every 5 minutes during the procedure till the end:
- Sedation score using RSS [23].
Hemodynamic profile (HR, MAP) 
Respiratory parameters (RR, SpO2)

During the procedure, any desaturation or apnoea were recorded when the SpO2 dropped to <90% or recorded cessation of respiration for 15 s or more, respectively, and were managed by supporting the airway and/or assisting ventilation. Hypotension was considered when the mean arterial pressure (MAP) fell below 60mmHg and managed by fluid bolus and/or vasopressors. Bradycardia was considered when heart rate was less than 60 beats per minute and managed with atropine 0.6 mg IV.

Propofol infusion was stopped once the procedure is done and patients were shifted to post-anesthesia care unit once the RSS score is 3. Total amount of Propofol consumption was noted. In the post anesthesia care unit, along with the above parameters (HR, MAP, RR, SpO2, Sedation score), patients were also monitored for recovery score using modified Aldrete score [24] (A score of 9-10 is acceptable) for every 15 minutes for an hour as per our hospital protocol before shifting to ward. In the PACU, patient satisfaction was noted. In the post anesthesia care unit, along with the above parameters (HR, MAP, RR, SpO2), Sedation score was measured using Visual Analogue Scale. Patients were also monitored for emergence (psychomotor agitation), post-operative nausea and vomiting and were managed accordingly.

Statistical Tools
The information collected regarding all the selected cases were recorded in a Master Chart in an Excel sheet. Data analysis was done with the help of computer using SPSS Statistical package version 20.0. t' test was used to test the significance of difference between quantitative variables and Chi-square test for qualitative variables. A p-value less than 0.05 denote a significant relationship. Demographic characteristics of cases studied, outcome variables and the significance of the differences between the outcome variables of the two groups were analyzed using the above tests.

Results

Table 1: Distribution of demographic and ASA between the groups

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>KP</th>
<th>FP</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0</td>
<td>1</td>
<td>0.749 (NS)</td>
</tr>
<tr>
<td>21-30</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>31-40</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>KP</th>
<th>FP</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>13</td>
<td>14</td>
<td>0.795 (NS)</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ASA</th>
<th>KP</th>
<th>FP</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>11</td>
<td>0.598 (NS)</td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

| Total            | 30 | 30 |         |

There was no statistically significant difference in the age wise distribution of patients between the groups (p=0.749). There is no statistically significant difference in the ASA class distribution among the groups (p=0.598).

Table 2: Comparison of Aldrete score, Sedation score & VAS between the groups

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>KP</th>
<th>FP</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 00mins</td>
<td>8.57±0.504</td>
<td>8.63±0.49</td>
<td>0.605 (NS)</td>
</tr>
<tr>
<td>At 15mins</td>
<td>9.03±0.183</td>
<td>9.34±0.466</td>
<td>0.006 (Sig.)</td>
</tr>
<tr>
<td>At 30mins</td>
<td>9.5±0.509</td>
<td>9.8±0.407</td>
<td>0.015 (Sig.)</td>
</tr>
<tr>
<td>At 45mins</td>
<td>9.97±0.183</td>
<td>10±0.00</td>
<td>0.326 (NS)</td>
</tr>
<tr>
<td>At 60mins</td>
<td>10±0.000</td>
<td>10±0.000</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sedation Score</th>
<th>KP</th>
<th>FP</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 00mins</td>
<td>3±0.000</td>
<td>3±0.000</td>
<td>-</td>
</tr>
<tr>
<td>At 15mins</td>
<td>2.9±0.305</td>
<td>2.5±0.509</td>
<td>0.001 (Sig.)</td>
</tr>
<tr>
<td>At 30mins</td>
<td>2.23±0.43</td>
<td>2.1±0.305</td>
<td>0.172 (NS)</td>
</tr>
<tr>
<td>At 45mins</td>
<td>2±0.000</td>
<td>2±0.000</td>
<td>-</td>
</tr>
<tr>
<td>At 60mins</td>
<td>2±0.000</td>
<td>2±0.000</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VAS</th>
<th>KP</th>
<th>FP</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7±0.183</td>
<td>7±0.183</td>
<td>0.694 (NS)</td>
</tr>
<tr>
<td>1</td>
<td>9±0.183</td>
<td>9±0.183</td>
<td>0.694 (NS)</td>
</tr>
</tbody>
</table>

The Aldrete score was more and significant in FP group at 15 min (p=0.006), 30 min (p=0.015) and it could not be measured at 60 min. The sedation score was significant in KP group at 15 min (p=0.001) and it could not be measured at 0, 45 and 60 min. There was no statistically significant difference in the VAS (p=0.694).

Table 3: Distribution of complications between the groups

<table>
<thead>
<tr>
<th>Hypotension</th>
<th>KP</th>
<th>Percentage</th>
<th>FP</th>
<th>Percentage</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Given</td>
<td>0</td>
<td>0.00%</td>
<td>1</td>
<td>10.00%</td>
<td>0.076 (NS)</td>
</tr>
<tr>
<td>NIL</td>
<td>30</td>
<td>100.00%</td>
<td>27</td>
<td>90.00%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assisted Ventilation</th>
<th>KP</th>
<th>Percentage</th>
<th>FP</th>
<th>Percentage</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL</td>
<td>1</td>
<td>3.30%</td>
<td>2</td>
<td>6.70%</td>
<td>0.554 (NS)</td>
</tr>
<tr>
<td>29</td>
<td>96.70%</td>
<td></td>
<td>28</td>
<td>93.30%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bradycardia</th>
<th>KP</th>
<th>Percentage</th>
<th>FP</th>
<th>Percentage</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>0</td>
<td>0.00%</td>
<td>4</td>
<td>13.30%</td>
<td>0.038 (Sig.)</td>
</tr>
<tr>
<td>NIL</td>
<td>30</td>
<td>100.00%</td>
<td>26</td>
<td>86.70%</td>
<td>0.038 (Sig.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inadequate Sedation</th>
<th>KP</th>
<th>Percentage</th>
<th>FP</th>
<th>Percentage</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL</td>
<td>30</td>
<td>100.00%</td>
<td>26</td>
<td>86.70%</td>
<td>0.038 (Sig.)</td>
</tr>
<tr>
<td>Propofol Given</td>
<td>0</td>
<td>0.00%</td>
<td>4</td>
<td>13.30%</td>
<td>0.038 (Sig.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PONV</th>
<th>KP</th>
<th>Percentage</th>
<th>FP</th>
<th>Percentage</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL</td>
<td>28</td>
<td>93.30%</td>
<td>30</td>
<td>100.00%</td>
<td>0.150 (NS)</td>
</tr>
<tr>
<td>Present</td>
<td>2</td>
<td>6.70%</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100%</td>
<td>30</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
Graph 1: Mean heart rate (bpm)

Graph 2: Mean MAP (mm Hg)

Graph 3: Mean SpO2 (in percentage)
Discussion
Akbulut UE, et al. (2016) [25] conducted a study to compare the efficacy and safety of Midazolam plus Ketamine versus Fentanyl plus Propofol combination administered to children (aged between 4-17 years) undergoing upper gastrointestinal endoscopy (UGE) to determine the most appropriate sedation protocol. They found complications in both the groups which made us exclude patients who are below 18 years in our study.

According to Yang JF, et al. (2016) [9], S. Muller, et al. (2004) [26] studies, patients aged more than 60 yrs and ASA class ≥ 3 had sedation related adverse effects. Thus, we have excluded patients above 60yrs and ASA class ≥ 3.

As Ketamine maintains spontaneous ventilation without effecting cardiopulmonary functions, Ketamine plus Propofol combination will provide better sedation and hemodynamic profile without effecting respiratory parameters, better recovery and fewer side effects.

Traditionally Propofol has been used in combination with Fentanyl to attain adequate levels of sedation and analgesia and is compatible with the procedure. Propofol with rapid recovery profile produces sedation and amnesia and has been increasingly used worldwide as a sedative agent for standard endoscopy [10-16]. But it has been observed that Propofol is associated with complications such as hypotension, respiratory depression, arterial oxygen desaturation, bradycardia, nausea and vomiting [2, 17-19] when used in combination with Fentanyl.

A study conducted by LL Bo, et al. (2011) [27] showed that Propofol sedation results in short recovery without cardio pulmonary side effects. Thus, we have included Propofol as an agent for sedation in our study in both the groups.

Fentanyl, a short-acting opioid, is useful for upper gastrointestinal endoscopic procedures and produces analgesia and sedation [21, 22]. According to Thomson A, et al. (2010) [8] Fentanyl with Midazolam produces shorter recovery time as compared to Meperidine with Midazolam with no difference in pain perception and hence Fentanyl was included in our study.

Benzodiazepines like Midazolam or Diazepam are commonly used to provide amnesia and alleviate anxiety. A study conducted by Mc Quaid, et al. (2008) [22] showed that Midazolam provided superior patient satisfaction than Diazepam and less frequent memory of events. So, we have included Midazolam in our study to alleviate anxiety and to provide amnesia.

Ketamine, a synthetic phencyclidine derivative, has been pronounced as a safe and effective sedative agent. Ketamine produces a dissociative state, combination of analgesia, amnesia and sedation at sub-anesthetic dose with minimal effects on the airway and vital reflexes. Studies conducted by Aydogan H, et al. (2013) [19], Daabis M, et al. (2009) [38], Willman EV, et al. (2006) [28], Akin A, et al. (2005) [29] showed that Ketamine Propofol (Ketofol) combination resulted in adequate sedation and analgesia without hemodynamic and respiratory depression (or) psychomimetic side effects and appears to be useful and can be safely used for procedural operations in ambulatory setting. Thus, we have included Ketamine in our study.

KP Group: Ketamine bolus was given at 1mg/kg and Propofol bolus was given at 0.5 µg/kg, followed by maintenance dose of Propofol infusion given at 50 µg/kg/min.

FP Group: Fentanyl bolus was given at 1.5µg/kg and Propofol bolus was given at 0.5 µg/kg, followed by maintenance dose of Propofol infusion given at 50µg/kg/min.

Patients were continuously monitored for hemodynamic profile (HR, MAP), respiratory profile (RR, SpO2), incidence of apnoea and desaturation for every 5min during the procedure and every 15min after the procedure for one hour.

During the procedure mean HR was more and was significant in KP group as compared to FP group at time intervals ranging from 5 – 40min (p<0.001). Post procedure, mean HR was more and it was significant in KP group than FP group at time intervals 0-45mins (p<0.001, Table 17). During the procedure mean MAP was more and significant in KP group as compared to FP group at time intervals ranging from 5 – 45mins (5-40 (p<0.001)); 45mins (p=0.002), Table 13. Post procedure, mean MAP was more and significant in KP group than FP group at time intervals ranging from 0-60mins (p<0.001).

It is comparable to the studies conducted by BahramiGorji F, et al. in (2016) [27] and Chowdhary IH, et al. (2017) [21]. In BahramiGorji F, et al. [27] study (Propofol- Fentanyl (PF) Versus Propofol-Ketamine (PK)) they found PK group had higher blood pressure in the eighth minute (p<0.05). In Chowdhary IH, et al. [21] (Ketamine- Diazepam (KD) versus Propofol-Fentanyl (PF)) they found incidents of hypertension, tachycardia, agitation, night mares and mean recovery time were observed to be more with KD group than PF group (p>0.001). However, it was not a major concern in our study as we have included only ASA grade I and II patients. Further, it is a well-known fact that the moderate increase in MAP could be related to the

Graph 4: Mean RR (per minute)
sympathomimetic effect of Ketamine. During the procedure mean RR was more and significant in KP group as compared to FP at time intervals ranging from 5–45min (5-35 (p=0.001); 40min (p=0.001); 45min (p=0.038). Post procedure, mean RR was more and significant in KP group than FP group (0min (p<0.001) and 30 min (p=0.037).

During the procedure mean SpO2 was comparable and it was not significant between the groups. Post procedure, mean SpO2 was more and significant in KP group than FP group (45mins (p=0.048) and 60mins (p=0.02). It is comparable to the study conducted by Akin A, et al. (2005) [41]. (Propofol versus Propofol–Ketamine), which says, addition of low dose Ketamine to Propofol reduced the risk of respiratory depression.

Propofol consumption
Patients with signs of inadequate sedation were supplemented with Propofol bolus doses at 0.5mg/kg. Mean Propofol consumption was more and significant in FP group than KP (p=0.001).

It was comparable to the study conducted by Hasanein R, et al. (2013) [3] (Ketamine-Propofol (KP) versus Fentanyl-Propofol (FP)), which says, propofol consumed was significantly higher in group FP compared with group KP (p=0.001).

Post procedure patient satisfaction score (VAS)
Mean VAS score was comparable and not significant in both the groups (p=0.694). It is comparable to the study conducted by Hasanein R, et al. (2013) [3].

It is observed that KP group took longer time than FP to reach the acceptable recovery score. The Aldrete score was more and significant in FP group (15 min (p=0.006) and 30min (p=0.015). It could be because Ketamine takes longer time to clear from the body.

The incidence of hypotension was insignificant both during and post procedure (p=0.076, Table 25). However, the incidence of bradycardia was more in FP group as compared to KP group and was significant (p=0.038). Our results concur with the results of Hasanein R, et al. (2013) [3].

There is no statistically significant incidence of desaturation in between the groups (p=0.554). It is similar to study conducted by BahramiGorji F, et al. (2016) [30] and Akin A, et al. (2005) [29] which showed addition of low dose Ketamine to Propofol reduced the risk of respiratory depression. This is because Ketamine does not depress the airway reflexes and maintains spontaneous ventilation. There is no statistically significant incidence of PONV in between the groups (p=0.150). It is similar to the study conducted by Willman EV, et al. (2006) [28]. It could be because of antiemetic property of Propofol which reduces the incidence of PONV caused by Ketamine.

Emergence was not detected in any of the patients in both the groups. It is comparable with the study conducted by Daabis M, et al. (2009) [31] which says, Ketofol combination resulted in adequate sedation and analgesia without psychomimetic side effects.

Conclusion
Propofol-Ketamine combination provided sedation quality similar to Propofol-Fentanyl combination with better hemodynamic profile and fewer side effects. Hence Propofol- Ketamine combination can be safely used in patients undergoing ERCP.

Conflict of Interest
Not available

Financial Support
Not available

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