Alcohol 84 (2020) 21–25

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

# A nationwide randomized, double-blind, placebo-controlled physicians' trial of loxoprofen for the treatment of fatigue, headache, and nausea after hangovers

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ARTICLE INFO

*Article history:*
Received 13 April 2019
Received in revised form
25 October 2019
Accepted 28 October 2019

*Keywords:*
Hangover
Headache
Loxoprofen
Randomized controlled trial

ABSTRACT

Hangovers are associated with negative economic consequences due to decreased job performance or frequent visits to physicians. Thus, a new strategy for the alleviation of hangover-related symptoms is needed to avoid this detriment to society. The purpose of this nationwide randomized, double-blind, placebo-controlled physicians' trial was to evaluate the efficacy of loxoprofen sodium for the alleviation of fatigue, headache, and nausea after hangover. A total of 229 participants were randomized to receive loxoprofen sodium (60 mg once orally) or placebo. The study was closed when the first 150 participants (n = 74 in the loxoprofen vs. n = 76 in the placebo groups) experienced hangovers. The primary endpoint was set as the difference in severity of general fatigue before and 3 h after taking the test drugs and was evaluated using a visual analogue scale. Secondary endpoints included difference in severity of headache, nausea, and incidence of adverse events. The study participants were 34 (interquartile range; 30–39) years old, 92.0% were men, and both groups were comparable for baseline characteristics. The alleviation of general fatigue did not differ statistically between the loxoprofen and placebo groups (24 [14–49] vs. 19 [9–35], $p = 0.07$). However, the alleviation of headache was statistically greater in the loxoprofen group (25 [10–50] vs. 10 [2–30], adjusted difference 14, 95% confidence interval 8–21, $p < 0.001$), whereas, there was no difference in nausea (7 [0–27] vs. 10 [0–24], $p = 0.68$). The incidence of adverse symptoms such as epigastric discomfort was also comparable between groups (2.7% vs. 3.9%, $p = 0.25$). Loxoprofen sodium was effective for relieving headaches after hangovers but did not alleviate general fatigue or nausea.



## Introduction

An alcohol hangover is composed of a set of disturbing symptoms, such as headache and nausea, the day after drinking excessive alcohol (Jayawardena, Thejani, Ranasinghe, Fernando, & Verster, 2017; Pittler, Verster, & Ernst, 2005; Verster & Penning, 2010). Some physicians also include fatigue as a hangover-related symptom (Verster & Penning, 2010). A hangover is associated with negative economic consequences due to decreased job performance or frequent presentation for medical care. Therefore, evaluating a new strategy for the alleviation of these hangover-related symptoms may aid in avoiding its detrimental effects on society (Frone, 2006; Hindmarch, Land, & Wright, 2012; Jayawardena et al., 2017; Perez, Keijzers, Steele, Byrnes, & Scuffham, 2013; Pittler et al., 2005; Verster & Penning, 2010). However, there is no consensus

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https://doi.org/10.1016/j.alcohol.2019.10.006

about the effective treatment protocol for the alleviation of these symptoms despite some data with respect to the efficacy of prophylaxis being available (Frone, 2006; Hindmarch et al., 2012; Jayawardena et al., 2017; Perez et al., 2013; Pittler et al., 2005; Verster & Penning, 2010). In contrast, a web-based questionnaire circulated by one of the most popular commercial medical journals in Japan (Nikkei Medical, Tokyo, Japan) was completed by 2739 medical doctors and revealed that approximately 17.1% of respondents themselves take nonsteroidal anti-inflammatory drugs (NSAIDs) empirically to alleviate hangover symptoms (Tajima, 2015). It is intuitively understandable that cyclooxygenase blockage and the resultant inhibition of prostaglandin synthesis may relieve some of the symptoms of a hangover, considering that alcohol metabolites, such as acetaldehyde, can provoke inflammation that may be associated with some of these symptoms (Brooks & Day, 1991; Jayawardena et al., 2017; Kaivola, Parantainen, Osterman, & Timonen, 1983; Ong, Lirk, Tan, & Seymour, 2007). The purpose of this nationwide randomized, double-blind, placebo-controlled physicians' trial was to evaluate the efficacy of loxoprofen sodium for the alleviation of fatigue, headache, and nausea after hangover. Our experimental hypothesis was that loxoprofen sodium is effective for relieving headache, slightly effective for general fatigue, and ineffective for nausea.

## Methods

### *Study design*

This study was designed as a nationwide, randomized, double-blind, placebo-controlled physicians' trial. The flowchart of participant selection is shown in Fig. 1. Participants were recruited using social networking service (SNS) announcements via Facebook and Twitter, and through Yahoo! JAPAN and Nikkei Medical from August 2017 to May 2018. After voluntary web-based submissions from the participants, we issued identification (ID) to each participant for the use of electronic data capture (EDC). Then, the participants were asked to provide their informed consent and to submit basic personal information, which was followed by our internal review to check whether they met the inclusion and exclusion criteria. The pre-specified inclusion and exclusion criteria are shown in Supplementary Table 1. In summary, participants were recruited for the trial if they were medical doctors in Japan who could drink alcohol and might experience hangovers during the study period and had read and agreed to the study concept, design, and protocols in a web-based informed consent form. Participants were excluded from the trial if they had any significant medical history or past complications associated with an increased risk of adverse events, such as a history of peptic ulcer or routine usage of NSAIDs. When the participants completed data input on the EDC and met the pre-specified criteria, they were randomized to receive either loxoprofen sodium (60 mg once orally, Loxonin®, Daiichi-Sankyo, Tokyo, Japan) or placebo, in a gender-stratified 1:1 manner. The test drugs were delivered to their institutions, and they were expected to take them whenever they experienced general fatigue related to a hangover. The symptoms before and 3 h after taking the medicine were recorded on the EDC. The study was led by the Japan Society of Clinical Research (JSCR). The study protocol, which complied with the standards outlined in the Declaration of Helsinki, was approved by the Institutional Review Board of the JSCR (approval number 201702), and was registered to the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR, Clinical Trial Registration Number UMIN000028441 01/08/2017, Hangovercome Study) which is certified by the International Committee of Medical Journal Editors (ICMJE).

### *Endpoint and sample size calculation*

The primary endpoint was set as the difference in severity of general fatigue before and 3 h after taking the test drugs. Secondary endpoints included difference in the severity of headache and nausea before and 3 h after taking the test drugs, and incidence of an adverse event. These symptoms were evaluated using a visual analogue scale (VAS) rating system with no symptoms taken to be 0 mm, placed at the left end of the VAS line, and the worst symptoms as 100 mm at the right end of the VAS line. Based on the drug information, according to which the time to maximum concentration of loxoprofen sodium in the blood is 0.45 h after the oral administration and its half-life is 1.22 h among healthy volunteers, we set the timing of symptom evaluation at 3 h after the test drug administration.

Sample size was determined based on the following estimates and indices: (1) the difference in the severity of the primary endpoint between the loxoprofen and placebo groups was estimated to be greater than 7 mm on the VAS rating system, (2) the standard deviation of the difference in severity of the primary endpoint was estimated to be 13.79 mm based on the preliminary web-based questionnaire, and (3) the statistical significance was evaluated using a $t$ test with a two-sided significance level of 0.05 and a statistical power of 0.80. In each group, 62 participants were needed to satisfy the above statistical requirements and we set the final sample size at 75 participants in each group, considering a maximum of 17.5% risk of inaccurate data input because of the symptoms of a hangover. In addition, we decided to continue the entries for the study until the number of randomization participants reached was 500 (250 in each group), because not all participants necessarily experienced a hangover during the study period (Fig. 1). Our pre-specified study completion point occurred when 150 participants experienced hangovers, took test drugs, and completed the EDC data input without any missing data. At this time point, the EDC was closed and an announcement that the study was complete was made by sending e-mails as well as through SNS announcements.

### *Statistical analysis*

Continuous variables were summarized using the median with 1st and 3rd quartiles. Categorical variables were summarized using frequencies with percentages. The difference in the effects of the treatment was analyzed by the linear regression model. In this model, the explained variable was the score of the VAS rating system at 3 h after the drug administration, and the explanatory variables were treatment with the drug, participant's sex, and VAS score before the drug administration. Fisher's exact test was applied to evaluate the independence of incidence of adverse events between the loxoprofen and placebo groups. There were no missing data in the present study. The significance level for our statistical analysis was set at 0.05 with the two-sided alternative hypothesis as the primary endpoint. $p$ values for the results of hypothesis testing for the secondary endpoints were evaluated by the Bonferroni adjustment for multiplicity of the tests, and the significance level was set at 0.017. All statistical analyses were performed using the R software (version 3.4.2).

## Results

The flowchart of participant selection and final study population for statistical analysis is shown in Fig. 1. During the study period, a total of 320 participants completed the web-based entry, and 297 were issued ID for EDC usage. After excluding 9 disqualified participants and 59 participants who did not complete the basic

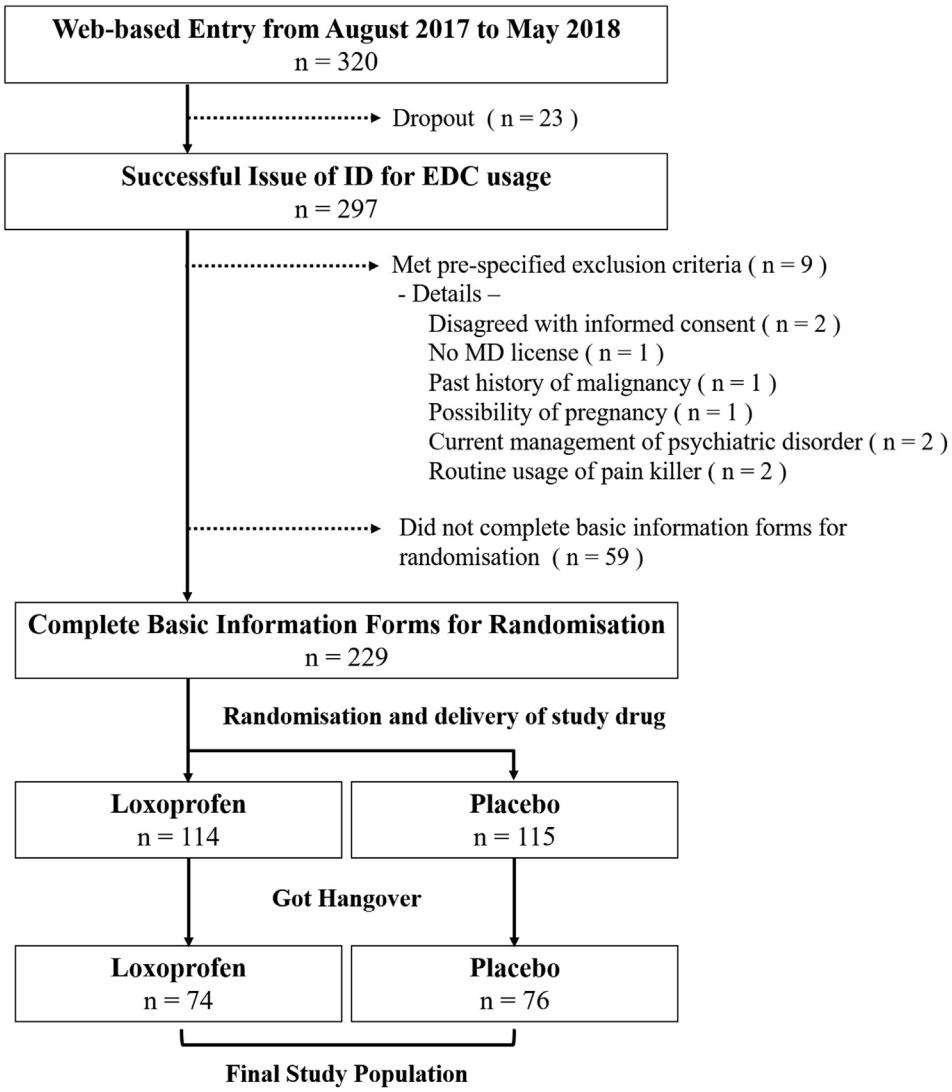


**Fig. 1.** Flowchart of participant selection. EDC, electronic data capture; ID, identification; MD, medical doctor

information forms, 229 participants were randomized between the loxoprofen sodium and the placebo groups, in a sex-stratified 1:1 fashion. Finally, 150 participants (n = 74 in the loxoprofen group vs. n = 76 in the placebo group) experienced hangovers, took the test drugs, and completed the data input. The geographical distribution and specialty of participants are shown in Supplementary Fig. 1 and Supplementary Table 2, respectively.

Participant characteristics are shown in Table 1. Study participants were 34 (interquartile range; 30–39) years old and 92.0% were men. Four (2.7%) participants took routine medication that might have interacted with loxoprofen sodium, and 45.3% worked at the University. Approximately 40% of the participants had ever used loxoprofen sodium for the alleviation of the symptoms related to a hangover, and more than 50% of them thought that it was effective for general fatigue, more than 90% for headache, and more than 20% of participants thought it was effective for nausea. Median water intake after drug administration was 300 (200–500) mL. Both groups were comparable for baseline characteristics (Table 1).

With respect to the hangover symptoms shown in Table 2, alleviation of general fatigue did not differ statistically between the loxoprofen and the placebo groups (24 [14–49] vs. 19 [9–35], adjusted difference 6, 95% confidence interval [CI] −0.49–13, $p = 0.07$). However, the rate of alleviation of headache was statistically greater in the loxoprofen group than in the placebo group (25 [10–50] vs. 10 [2–30], adjusted difference 14, 95% CI 8–21, $p < 0.001$), whereas that of nausea was not statistically different (7 [0–27] vs. 10 [0–24], adjusted difference −1, 95% CI −6–4, $p = 0.68$). The incidence of adverse symptoms was also comparable between the loxoprofen and placebo groups, with two participants with epigastric discomfort reported in the loxoprofen group, two participants with stomach aches, and one with a feeling of a loose tooth were reported in the placebo group ($p = 0.25$) (Table 2).

## Discussion

In this nationwide randomized, double-blind, placebo-controlled physicians' trial of loxoprofen sodium for the alleviation of the symptoms after a hangover, we demonstrated that (1) statistically, loxoprofen sodium did not alleviate general fatigue or nausea symptoms when compared to placebo, whereas loxoprofen was significantly effective for relieving headache, even after adjustments for sex and baseline severities of symptoms were made; and (2) the incidence of adverse events was comparable between the loxoprofen and placebo groups.

**Table 1**
Participants' backgrounds.

| Parameter | Total (n = 150) | Loxoprofen (n = 74) | Placebo (n = 76) |
|---|---|---|---|
| Age, years | 34 (30–39) | 33 (30–37) | 35 (32–40) |
| Male | 138 (92.0) | 68 (91.9) | 70 (92.1) |
| Height, cm | 171 (167–175) | 172 (168–175) | 171 (167–175) |
| Weight, kg | 67 (61–73) | 67 (62–72) | 66 (60–73) |
| Medication with possible interaction with loxoprofen sodium | 4 (2.7) | 3 (4.1) | 1 (1.3) |
| ACEI or ARB | 4 (2.7) | 3 (4.1) | 1 (1.3) |
| Thiazide | 1 (0.7) | 1 (1.4) | 0 (0.0) |
| Work at University | 68 (45.3) | 35 (47.3) | 33 (43.4) |
| Expectation of study drug | | | |
| Identified | 20 (13.3) | 10 (13.5) | 10 (13.2) |
| Non-identified, including unknown | 130 (86.7) | 64 (86.5) | 66 (86.8) |
| Experience in using loxoprofen for managing symptoms of hangover | 64 (42.7) | 33 (44.6) | 31 (40.8) |
| Believe it is effective for fatigue | 36 (56.3) | 17 (51.5) | 19 (61.3) |
| Believe it is effective for headache | 58 (90.6) | 30 (90.9) | 28 (90.3) |
| Believe it is effective for nausea | 13 (20.3) | 8 (24.2) | 5 (16.1) |
| Alcohol (multiple selection) | | | |
| Beer | 133 (88.7) | 65 (87.8) | 68 (89.5) |
| Wine | 55 (36.7) | 30 (40.5) | 25 (32.9) |
| Whisky or brandy | 39 (26.0) | 18 (24.3) | 21 (27.6) |
| Japanese sake | 57 (38.0) | 29 (39.2) | 28 (36.8) |
| Japanese shochu | 25 (16.7) | 12 (16.2) | 13 (17.1) |
| Others, including cocktails | 22 (14.7) | 9 (12.2) | 13 (17.1) |
| Water intake after study drug administration, mL | 300 (200–500) | 300 (200–500) | 300 (150–500) |

Continuous variables were summarized using the median with 1st and 3rd quartiles in parentheses. Categorical variables were summarized by frequencies with percentages in parentheses. The following drugs are listed as drugs that may interact with NSAIDs according to drug information: warfarin, ACEI or ARB, new quinolones, methotrexate, lithium, thiazide, and sulfonylurea.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

*Management of hangover*

As there is no consensus about the effective treatment protocol for the alleviation of the symptoms of a hangover, despite some data with respect to the efficacy of prophylaxis being available, our results confirmed that loxoprofen can be used for headache relief, although it was already empirically known by 17.1% of physicians based on a web-based questionnaire, as mentioned in the introduction (Frone, 2006; Hindmarch et al., 2012; Jayawardena et al., 2017; Kaivola et al., 1983; Perez et al., 2013; Pittler et al., 2005; Tajima, 2015; Verster & Penning, 2010). There is a wide range of symptoms associated with a hangover, and many possible mechanisms have been suggested for these symptoms (Frone, 2006; Hindmarch et al., 2012; Jayawardena et al., 2017; Kaivola et al., 1983; Perez et al., 2013; Pittler et al., 2005; Tajima, 2015; Verster & Penning, 2010). Our experimental hypothesis was that loxoprofen sodium is effective for relieving headache, slightly effective for general fatigue, and ineffective for nausea. This hypothesis was developed empirically, considering that cyclooxygenase blockage and the resultant inhibition of prostaglandin synthesis can relieve hangover symptoms provoked by inflammation due to alcohol metabolites, although there is no strong scientific evidence regarding possible mechanisms for the pathology of alcohol hangover (Brooks & Day, 1991; Jayawardena et al., 2017; Kaivola et al., 1983; Ong et al., 2007; Verster & Penning, 2010). However, according to our results, loxoprofen sodium was only effective for headaches. This is partly because of multiple physiological mechanisms responsible for causing hangovers, such as those associated with metabolism of alcohol itself or the oxidative damage caused by the free radicals associated with excessive alcohol consumption (Jayawardena et al., 2017; Pittler et al., 2005; Verster & Penning, 2010). Even though our study first revealed that loxoprofen sodium is effective to alleviate headaches during a hangover, it is important to remember that we do not intend to recommend alcohol consumption through this study, and that the misuse of alcohol is an important issue that should be discussed with respect to interventions such as behavioral counseling (U.S. Preventive Services Task Force, 2004).

**Table 2**
Primary and secondary endpoints of hangover.

| Parameter | Loxoprofen (n = 74) | Placebo (n = 76) | *p* value |
|---|---|---|---|
| General Fatigue | | | |
| Pre | 70 (59–75) | 70 (60–80) | – |
| 3 h later | 30 (17–60) | 50 (20–60) | – |
| Delta | 24 (14–49) | 19 (9–35) | 0.07 |
| Headache | | | |
| Pre | 60 (26–71) | 54 (24–70) | – |
| 3 h later | 10 (0–31) | 24 (0–58) | – |
| Delta | 25 (10–50) | 10 (2–30) | <0.001 |
| Nausea | | | |
| Pre | 25 (1–60) | 30 (10–60) | – |
| 3 h later | 9 (0–24) | 7 (0–34) | – |
| Delta | 7 (0–27) | 10 (0–24) | 0.68 |
| Adverse Symptoms | | | 0.25 |
| Stomach ache | 0 (0.0) | 2 (2.6) | – |
| Epigastric discomfort | 2 (2.7) | 0 (0.0) | – |
| Feeling of loose tooth | 0 (0.0) | 1 (1.3) | – |

Continuous variables were summarized using median with 1st and 3rd quartiles in parentheses. Categorical variables were summarized by frequencies with percentages in parentheses.

*Clinical implications*

When implementing a new treatment strategy in medicine, we must think about the balance of therapeutic efficacy, safety, cost, and the overall effect of the treatment on the economy of the country. We showed that loxoprofen sodium showed statistically more alleviation of headache than placebo, 3 h after the administration of the drug. The incidence of adverse events was 2.7% in this study, and was a transient epigastric discomfort. Even without definite evidence regarding the incidence of adverse events of a single dose of NSAIDs in healthy non-risk populations, adverse events are assumed to be minimal for loxoprofen sodium, which is a derivative of propionic acid, which includes ibuprofen (Ong et al., 2007; Rollason, Samer, Daali, & Desmeules, 2014). The familiarity

with NSAIDs and their adverse events in the medical community may also ensure the safe usage of this drug (Ong et al., 2007; Rollason et al., 2014). In addition, the cost of loxoprofen sodium (60 mg) was less than $0.50 per tablet. With respect to the adverse economic effects of a hangover, it was reported that approximately $2000 per employee are lost annually because of alcohol-related absenteeism and impaired working ability in the United States (Jayawardena et al., 2017; Verster & Penning, 2010). With these points of view, we think that the health and economic benefits outweigh the potential harm of treating headaches due to hangovers using NSAIDs. This strategy for alleviation of headaches due to hangovers using NSAIDs may, at least in part, contribute to avoiding the detriment to society associated with negative economic consequences due to decreased job performance or frequent presentation to a health care provider (Frone, 2006; Hindmarch et al., 2012; Jayawardena et al., 2017; Perez et al., 2013; Pittler et al., 2005; Verster & Penning, 2010).

### *Study limitations*

Our study has some limitations that warrant mention. First, the difference in the effects of loxoprofen sodium as a treatment for hangover-related symptoms with respect to the sex of the participants could not be determined because less than 10% of the participants enrolled in this study were women. Second, it is possible that a dose of 60 mg by oral administration may be a minimal dose and that high dose administration may lead to different results. Third, it is possible that evaluation at 1 or 2 h after the test drug administration may also lead to different results, considering the rapid absorption and fast metabolic pharmacokinetics of loxoprofen sodium. Fourth, variation in therapeutic and adverse responses of different NSAIDs has been reported, and it is unclear whether our results with loxoprofen sodium can be applied to other NSAIDs (Fries et al., 2006; Rollason et al., 2014). Fifth, there is no strong scientific evidence regarding possible mechanisms for the pathology of alcohol hangover, and the most important theories are the authors' hypotheses, not a consensus in the field (Verster & Penning, 2010). Sixth, due to a problem of multiplicity of the statistical tests and the above-mentioned lack of pathological evidence, we wanted to minimize the number of endpoints as much as possible. This led to a narrow focus on hangover symptoms. Lastly, amount of alcohol consumption or genetic susceptibility for alcohol were not evaluated. However, lack of these measurements is not of great importance because the merit of randomized controlled trial is to balance all confounding factors regardless of measurability. Thus, we believe that a nationwide randomized, double-blind, placebo-controlled trial with comparable baseline characteristics between the loxoprofen and placebo groups outweighs these limitations.

## Conclusions

This nationwide randomized, double-blind, placebo-controlled physicians' trial demonstrated that loxoprofen sodium was effective for relieving headache during a hangover but did not alleviate general fatigue or nausea.

## Funding

We utilized a crowd-funding service to secure a part of research funds (Fanfare, Osaka, MEDICUS SHUPPAN,Publishers Co.,Ltd.). Otherwise, this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Data sharing statement

The anonymized data set with identifiers of participants are available online as Supplementary material of the manuscript.

## Author contributions

Masahiko Hara, Kenichi Hayashi, Tetsuhisa Kitamura, Michitaka Honda, and Masatake Tamaki contributed to the conception and design of the work, the acquisition, analysis, and interpretation of data, and drafting or revising the manuscript critically for important intellectual content.

## Declaration of Competing Interest

All authors have no conflicts of interest to declare.

## Acknowledgments

We thank Ken Tajima, Aya Masutani, and Mamoru Ichikawa for their support in expanding our project through the medium of internet.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alcohol.2019.10.006.

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