Efficacy of Ibuprofen Gargle for Postoperative Pain After Mandibular Third Molar Extraction: A Phase II, Placebo-Controlled, Double-Blind, Randomized Crossover Trial

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Study Protocol

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Abstract

Background

Extraction of mandibular third molars is one of the most commonly performed oral surgical procedures, and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for pain management. Oral administration of NSAIDs produces various adverse events such as gastrointestinal disorders, renal and hepatic dysfunction, and platelet dysfunction. Topical use of analgesics has been proposed as an alternative to oral and injectable medications to safely improve postoperative pain relief. We will conduct a single-center, placebo-controlled, double-blind, randomized crossover trial to assess the pain-relieving effect of an ibuprofen-containing gargle in patients undergoing extraction of mandibular third molars in comparison with a placebo gargle.

Methods

This study will be performed at Kobe University Hospital. Participants (n = 40) will be randomized equally to one of two groups. The IP group will receive ibuprofen gargle on postoperative day (POD) 1 and placebo gargle on POD 2. The PI group will receive placebo gargle on POD 1 and ibuprofen gargle on POD 2. Both groups will receive ibuprofen gargle on PODs 3 to 5 at least once daily. The primary objective is to estimate the within-subject difference in a visual analogue scale (VAS) before and 5 minutes after use of ibuprofen or placebo gargle on PODs 1 and 2. The secondary objectives are to estimate the within-subject difference in ΔVAS before and 15 minutes after use of ibuprofen or placebo gargle on PODs 1 and 2, the ΔVAS before and after 5 or 15 minutes of use of ibuprofen gargle on PODs 3 to 5, the overall effectiveness (self-completion, five scales) on PODs 1 to 5, the daily frequency of use (ibuprofen or placebo gargle and analgesics) on PODs 1 to 7, and the occurrence of adverse events.

Discussion

This will be the first well-designed clinical study to evaluate the efficacy of ibuprofen gargle for relieving postoperative pain after extraction of mandibular third molars. This trial will provide exploratory evidence of the efficacy and safety of ibuprofen gargle for pain reduction after mandibular third molar extraction.

Trial registration

Japan Registry of Clinical Trials (jRCT) identifier: jRCTs051210022. Registered on 10 May 2021.

Background

Extraction of the mandibular third molar is one of the most commonly performed oral surgical procedures [1, 2]. Because of the high degree of invasiveness when bone removal and crown division are involved, moderate to severe postoperative complications such as pain, swelling, difficulty in opening and swallowing [2, 3], and postoperative difficulty in oral intake may occur.

Post-extraction pain is one of the most common and important postoperative complications, and is the reason why many patients avoid treatment [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the accepted analgesics for the treatment of post-extraction pain, and acidic NSAIDs are usually chosen for moderate pain, such as in the case of mandibular extractions. In patients with gastrointestinal ulcers or aspirin-induced asthma, acetaminophen may be used as an alternative drug [4]. NSAIDs such as celecoxib [5], valdecoxib [6] and ibuprofen [7] and opioid-containing drugs such as oxycodone [8] have been studied to identify the optimal analgesics for pain relief in mandibular third molar extractions. In a systematic review of 21 high-quality clinical trials, Weil et al. reported that oral paracetamol (acetaminophen) was safe and effective in the treatment of postoperative pain after extraction of embedded mandibular third molars [9], and Bailey et al. reported in a Cochrane review of 2241 patients that oral ibuprofen was superior to oral paracetamol in the treatment of postoperative pain [10].

Side effects should be considered when prescribing analgesics in the postoperative period, with opioids mainly associated with respiratory depression, nausea and vomiting, and constipation [11], and NSAIDs with gastrointestinal disorders, renal and hepatic dysfunction, and platelet dysfunction [12]. Topical use of analgesics has been proposed as an alternative to oral and injectable medications to safely improve postoperative pain relief [13, 14]. Topical administration has also been reported to reduce side effects without reducing the quality of analgesia [15].

Ibuprofen, developed in the 1960s, is a potent inhibitor of prostaglandin synthesis and reduces fever, pain, and inflammation [16]. Because ibuprofen is pharmacologically active against both cyclooxygenase (COX)-1 and COX-2, adverse effects such as gastrointestinal and renal dysfunction may occur after systemic administration. However, several reviews and meta-analyses have shown that ibuprofen is effective in adults and children and is the least toxic of the NSAIDs [17, 18]. We hypothesized that an oral gargle containing dissolved ibuprofen (0.6% or 1.0%) that could be delivered directly to the affected area could contribute to pain relief for oral mucositis. It has been reported that there were no major safety concerns and that some pain relief was obtained for chemotherapy/chemoradiotherapy-associated oral mucositis [19].

In post-extraction wounds, the loss of keratinized mucosa associated with tooth extraction allows for rapid absorption and efficacy of topically administered medication in the affected area. It is hoped that ibuprofen-containing gargles will provide an efficient drug delivery system targeting the painful area after tooth extraction with minimal systemic effects. An unresolved limitation of the study is that it is not possible to estimate the extent to which a placebo effect may be present, as studies in healthy adults and patients with chemotherapy/chemoradiotherapy-associated oral mucositis have been conducted as uncontrolled trials.

Therefore, this clinical study is designed to evaluate the efficacy and safety of ibuprofen gargle for the purpose of relieving postoperative pain in patients with extracted mandibular third molars to assess

whether the pain-relieving effect of ibuprofen gargle can be confirmed without compromising the quality of post-extraction pain management in daily practice.

Objectives

Primary objective

The primary objective is to estimate the within-subject difference in a visual analogue scale (VAS) before and 5 minutes after use of ibuprofen or placebo gargle on postoperative days (PODs) 1 and 2 in patients undergoing mandibular third molar extractions in comparison with a placebo gargle (ΔVAS_5_ibuprofen - ΔVAS_5_placebo).

Secondary objectives

The secondary objectives are to evaluate the within-subject difference in ΔVAS 15 (ΔVAS 15_ibuprofen - ΔVAS15_placebo) before and 15 minutes after use of ibuprofen or placebo gargle on PODs 1 and 2, the ΔVAS before and after 5 or 15 minutes of use of ibuprofen gargle on PODs 3 to 5, the overall effectiveness (self-completion, five scales) on PODs 1 to 5, the daily frequency of use (ibuprofen or placebo gargle and analgesics) on PODs 1 to 7, and the occurrence of adverse events.

Methods

Study design

This study is designed as a single-center, placebo-controlled, double-blind, randomized crossover trial. The patient flowchart is shown in Figure 1.

Study setting

This study will be performed at Kobe University Hospital. All study data will be stored and archived in the data center at Kobe University Hospital.

Study population

Inclusion criteria

1. Patients planning to have a mandibular third molar extraction or who have had a mandibular third molar extracted within the last 24 hours.

2. Patients aged 20 years or older at the time of consent acquisition.

3. Patients for whom documented consent has been obtained regarding their voluntary participation in this clinical study.

Exclusion criteria

1. Patients with peptic ulcers.

2. Patients with concurrent severe or uncontrolled concomitant medical conditions.

3. Patients with a history of hypersensitivity to any component of the ibuprofen gargle.

4. Patients with impaired cardiac function or clinically significant heart disease.

5. Patients with aspirin-induced asthma.

6. Patients who use analgesic drugs at least once a week for any chronic pain.

7. Patients with dementia, psychiatric symptoms, drug addiction, or alcoholism.

8. Pregnant or lactating women.

9. Patients deemed inappropriate by the investigator.

Surgical procedure

All the surgeries should be performed by an experienced oral surgeon with a minimum of 3 years of post-graduate experience using the same protocol. Povidone iodine solution will be applied around the mouth; and 2% lidocaine + 1:80,000 epinephrine carpules will be used to block the inferior alveolar nerves. A mucoperiosteal envelope flap will be created using a standard incision. If needed, bone removal and tooth sectioning will be performed with a low-speed hand-piece under sufficient sterile solution irrigation. Following tooth removal, the socket will be irrigated with 10–20 ml saline, and the flap will be sutured using 2 to 3 resorbable sutures (3–0 Vicryl, Ehicon, Norderstedt, Germany). The operation time will be recorded in minutes from the time of incision to completion of the last suture. If needed, supplementary intraoperative local analgesia will be given and recorded. Loxoprofen (60 mg) will be prescribed, and the patients will be instructed to take up to three tablets daily.

Ibuprofen gargle / placebo gargle

The ibuprofen gargle was manufactured at the Department of Pharmacy, Kobe University Hospital. The gargle (100 mL) contains ibuprofen 600 mg (0.6%), sodium hydroxide, sodium hydrogen carbonate, hydrochloric acid (to regulate pH), glycerin, and flavor. The placebo gargle formulation is the same but without ibuprofen.

Intervention and treatment protocol

(1) IP group: ibuprofen gargle on POD 1, placebo gargle on POD 2, ibuprofen gargle on PODs 3–5 at least once daily.

(2) PI group: placebo gargle on POD 1, ibuprofen gargle on POD 2, ibuprofen gargle on PODs 3–5 at least once daily.

Dosage: Approximately 10 mL is dispensed into a measuring cup and held in contact with the affected area for at least 30 seconds (preferably 1 minute), then spat out and discarded.

Patients will not drink water or rinse their mouths for at least 5 minutes after the application.

As a general rule, patients will be allowed an interval of at least 15 minutes between uses of the study drug. The maximum daily dosage should be one bottle (100 mL).

Randomization (allocation)

Subjects will be randomly assigned to either the IP group or the PI group at a 1:1 allocation, using the permutation random block method stratified by category according to whether or not a maxillary third molar is to be extracted at the same time. The block size will not be disclosed to ensure that blinding is maintained. The allocation sequence for the randomization method will be generated by the biostatistician.

All subjects who provide consent to participate and who fulfil the inclusion criteria and do not meet any of the exclusion criteria will be randomized. The principal investigator or sub-investigator will send a subject enrollment form by e-mail to the data center. The staff at the data center will confirm the subject's eligibility and issue the subject enrollment confirmation form that contains the eligibility judgement, the randomization assignment result from the generated random sequence, and the enrollment number. Thereafter, the form will be sent to the principal investigator or sub-investigator.

Primary endpoint

Change in the within-subject VAS before and after 5 minutes of use of the first ibuprofen or placebo gargle on PODs 1 and 2 (ΔVAS_5_ibuprofen - ΔVAS_5_placebo).

Secondary efficacy endpoints

(1) ΔWithin-subject VAS before and 15 minutes after the first use of ibuprofen or placebo gargle on PODs 1 and 2 (ΔVAS_{15}_ibuprofen – ΔVAS_{15}_placebo).

(2) ΔVAS before and after 5 and 15 minutes of use of the first ibuprofen gargle on PODs 3 through 5.

(3) Overall daily efficacy on PODs 1 to 5.

(4) Number of uses (gargle, analgesic drug) per day on PODs 1 to 7.

Secondary endpoints for safety

(1) Presence or absence of adverse events associated with the conduct of this clinical study.

Time schedule of intervention, outcomes, and other assessments

The relationship among interventions, outcomes, other assessments, and visits for subjects in this study is shown in Table 1.

Table 1. Summary of study assessments and procedures

	STUDY PERIOD							
	Enrollment	Allocation	Post-allocation					Close-out
Time point	POD 0 (pre-extraction)	POD 0 (post-extraction)	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6-10
ENROLLMENT:								
Eligibility screen	X							
Informed consent	X							
Registration	X							
Surgical information (#1)	X	(X)						
Allocation		X						
INTERVENTIONS:								
I then P			●					
P then I				●				
I					●	●	●	
ASSESSMENTS:								
VAS (5 min)			X	X	(X)	(X)	(X)	
VAS (15 min)			X	X	(X)	(X)	(X)	
Diary (#2)			X	X	X	X	X	X
Adverse events			X	X	X	X	X	X

#1: Sex, age, reason for extraction, side of extraction, Pell-Gregory classification, Winter's classification

#2: Total amount of rescue medication, number of tablets, number of analgesic uses (gargles), self-reported global efficacy.

Data collection and management

The primary investigator or sub-investigator will enter the case report form (CRF) data for each subject into the electronic data capture (EDC) system. The principal investigator will confirm that the entered CRF data are complete and correct, electronically sign the CRF on the EDC system, and then make a printout of the signed CRF for filing. The CRF printout will be retained. If there are any queries about the CRF data that are entered by the staff at the data center, the primary investigator or sub-investigator should promptly respond to the queries.

Statistics

Sample size calculation

Target number of subjects and setting basis

The target number of subjects is 40: 20 subjects in the IP group, and 20 subjects in the PI group.

In a previous report on healthy subjects and patients with chemotherapy/chemoradiotherapy-associated oral mucositis [19], the mean ΔVAS and ΔVAS standard deviation (SD) of pain relief after 3 days of use were -1.28 and 0.84 (n = 7 patients), respectively; of which the pre-use VAS value of ibuprofen gargle was more than 3. In the subgroup with a VAS of 3 or more before ibuprofen gargle use, the ΔVAS was -1.56 and the ΔSD was 0.81 (n = 5).

In the present study, we estimate a ΔVAS_5 of -1.50 and ΔSD of 1.20 for ibuprofen gargles, and a ΔVAS_5 of -0.70 and a ΔSD of 1.20 for placebo gargles, assuming a placebo effect of less than half the ΔVAS_5 of ibuprofen gargles. Therefore, for a mean within-subject difference in ΔVAS_5 (ΔVAS_5_ibuprofen-ΔVAS_5_placebo) of 0.80, a common ΔSD of 1.20, a ratio of between and within-subjects variance of 0.8–1.2, an alpha error of 0.05, and a beta error of 0.1, we need a total of 30 cases. Considering a 30% potential withdrawal rate, we therefore plan to enroll 40 patients (20 per group).

Analysis

A summary of the planned statistical analysis for this study is provided below. The final analysis will be performed after data from the subjects have been obtained and locked at the end of the follow-up period.

The full analysis set (FAS) is the set of randomized subjects who receive at least one dose of the study drug and exclude those without baseline data or major protocol violations (e.g. absence of informed consent or enrollment outside the contract period). The per protocol set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol and excludes those with any of the following:

(1) violation of the inclusion criteria

(2) violation of the exclusion criteria

(3) missing primary endpoints.

The safety analysis set is the set of subjects who receive at least one dose of the study drug.

Handling of data

If there is any doubt about the data summarization or analysis, the biostatistician and the study representative will discuss the issue and decide how it will be handled. When missing data are identified, the researcher will inquire with the subject. If the within-subject difference or ΔVAS cannot be calculated due to missing VAS values, the within-subject difference or ΔVAS at that time will result in zero. If any missing or deficient values other than VAS values are not resolved, no completion will be performed.

(1) Primary analysis

In this study, the mean and SD of ΔVAS_5 on PODs 1 and 2 and, where appropriate, the 95% confidence interval (CI) of the mean will be calculated. We will also calculate the mean and SD of the within-study difference in ΔVAS_5 and, where appropriate, the 95% confidence interval of the mean. The treatment effect will be estimated by dividing the mean difference in the within-subject difference in ΔVAS_5 by 2 and calculating the p-value using an unpaired t-test.

(2) Secondary analysis

The mean and SD of ΔVAS_{15} on PODs 1 and 2 and, where appropriate, the 95% confidence interval of the mean will be calculated. We will also calculate the mean and SD of the within-study difference in ΔVAS_{15} and, where appropriate, the 95% confidence interval of the mean. The treatment effect will be estimated by dividing the mean difference in the within-subject difference in ΔVAS_{15} by 2 and calculating the p-value using an unpaired t-test.

ΔVAS before and 5 to 15 minutes after the first ibuprofen gargle use on PODs 3 to 5

The mean and 95% confidence intervals of ΔVAS_5 and ΔVAS_{15} for PODs 3 to 5 will be calculated for each group. An analysis of covariance with pre-use as a covariate will be used to calculate the adjusted ΔVAS_5 and ΔVAS_{15} and their 95% confidence intervals for each group.

Overall daily effectiveness for PODs 1 to 5

We will calculate summary statistics for overall daily efficacy on PODs 1 to 5, scale by scale, group by group.

Number of times of daily use of ibuprofen or placebo-containing rinses and analgesics in PODs 1 to 7

Summary statistics will be calculated for each group for the number of times ibuprofen or placebo-containing products and analgesics were used on PODs 1 to 7.

Adverse events

In our study, an adverse event is defined as any disease, disability, death, or infection that occurs during this study. The principal investigator or sub-investigator will record all the adverse events in the CRF and treat and follow the patient until resolution during the study. If the principal investigator or sub-investigator finds a potentially causal relationship to the study drug, all adverse events will be recorded to report to the review board.

Monitoring

Periodic monitoring of the study will be performed to check that the human rights and welfare of subjects are being protected, the study is being conducted safely in accordance with the protocol and the applicable regulatory requirements under the Clinical Trials Act, and the data are being collected properly. The principal investigator will appoint a responsible monitor and other monitors for the study. The items to be checked at monitoring are specified in the written procedure for implementation of study monitoring.

For quality assurance, the study will be examined to determine that it is being conducted in accordance with the protocol and written procedures, independently and separately from the routine activities of monitoring.

Discussion

This single-center, placebo-controlled, double-blind, randomized crossover trial will be the first well-designed clinical study to evaluate the efficacy of ibuprofen gargle for the purpose of relieving postoperative pain after extraction of mandibular third molars.

Mandibular third molars are commonly impacted, and postoperative pain is a major complication when they are extracted. Symptomatic pharmacological treatment aims to provide postoperative pain relief. Continuous medication with NSAIDs is recommended as the first-line treatment after extraction of mandibular third molars to relieve pain and inflammation. Oral administration of NSAIDs can lead to various adverse effects; therefore, topical NSAIDs are preferred to minimize these side effects [20,21]. The problem with administration of NSAIDs three times a day is that the analgesic effect wears off and post-extraction pain recurs. Several methods of treating intermittent pain with analgesic rinses have been reported in the past, but none have been approved in Japan. However, to date, there have been few well-designed clinical studies comparing the efficacy and safety of analgesic gargles to relieve postoperative pain after mandibular third molar extraction. Thus, the focus has recently been increased on the development of topically administered NSAIDs in the form of gels, toothpastes, and rinses [20,21]. However, few studies have shown the benefit of ibuprofen gargle for postoperative pain after tooth extraction.

We have reported that there were no major safety concerns and that some pain relief was obtained with an ibuprofen gargle in patients with chemo- or chemoradiotherapy-induced oral mucositis [19]. Ibuprofen gargles are retained in the mouth for about 1 minute and then spat out, so it is unlikely that ibuprofen will

be absorbed into the body. If the full amount of an ibuprofen gargle product (600 mg/100 mL) is used at the indicated dosage and method of administration, the amount of drug that could be ingested accidentally is less than the maximum daily allowance (600 mg) approved for oral ibuprofen. Therefore, it is estimated that adverse events due to ibuprofen absorbed orally are less than or equal to those reported for oral ibuprofen.

For ethical reasons, only actual ibuprofen-containing medication will be used after PODs 3–5. The reason for the crossover study between POD 1 and POD 2 was that the median duration of effect of the ibuprofen-containing gargle was about 20 minutes in previous studies, and there was no carryover effect in the study comparing POD 1 and POD 2. Therefore, we chose an ibuprofen gargle as the test drug for treating patients after mandibular third molar extraction, and decided that a study period of 5 days was a sufficient short-term treatment period. Adverse events and all conditions that occur will be recorded and observed until the condition resolves within the study period, regardless of a causal relationship with the clinical study.

However, because past clinical trials used only actual ibuprofen-containing drugs, this clinical trial was designed as a placebo-controlled comparative study to examine the placebo effect. We will therefore conduct a study of an ibuprofen gargle for postoperative pain after mandibular third molar extraction: a phase II, placebo-controlled, double-blind, randomized crossover trial.

This study will provide valuable evidence to support the use an ibuprofen gargle for patients after mandibular third molar extraction. Ibuprofen gargle may relieve the pain caused by mandibular third molar extraction.

Trial status

This manuscript is based on the current version of the study protocol (version 1.1, last updated on 1 March 2021). The study was first authorized on 1 March 2021. Participant recruitment will start on 1 June 2021. The expected date of completion (last visit of last patient) is 30 September 2022.

Abbreviations

CI, confidence interval

COX, cyclooxygenase

CRF, case report form

EDC, electronic data capture

FAS, full analysis set

GCP, good clinical practice

jRCT, Japan Registry of Clinical Trials

NSAIDs, non-steroidal anti-inflammatory drugs

POD, postoperative day

PPS, per protocol set

SD, standard deviation

VAS, visual analogue scale

Declarations

Ethics approval and consent to participate

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of good clinical practice (GCP), and all of the applicable regulatory requirements. Ethics approval is overseen by Kobe University Clinical Research Ethics Committee (reference number: C200024). Written informed consent will be obtained from all participants before any study procedure is performed. The participant will have the opportunity to review the participant consent form, and agree that they fully understand the details of the study procedures. Informed consent will be administered by a suitably qualified and experienced individual who has been delegated this duty by the principal investigator.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this study protocol as no datasets were generated.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YK is the chief investigator, conceived and designed the study, and drafted the manuscript. TIoroi obtained grant funding and designed the statistical analysis plan, managed the study, and reviewed the

manuscript. TIto managed the study and drafted the manuscript. YO, TH, IY, and MA reviewed the manuscript. All authors provided final approval of the manuscript.

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Figures

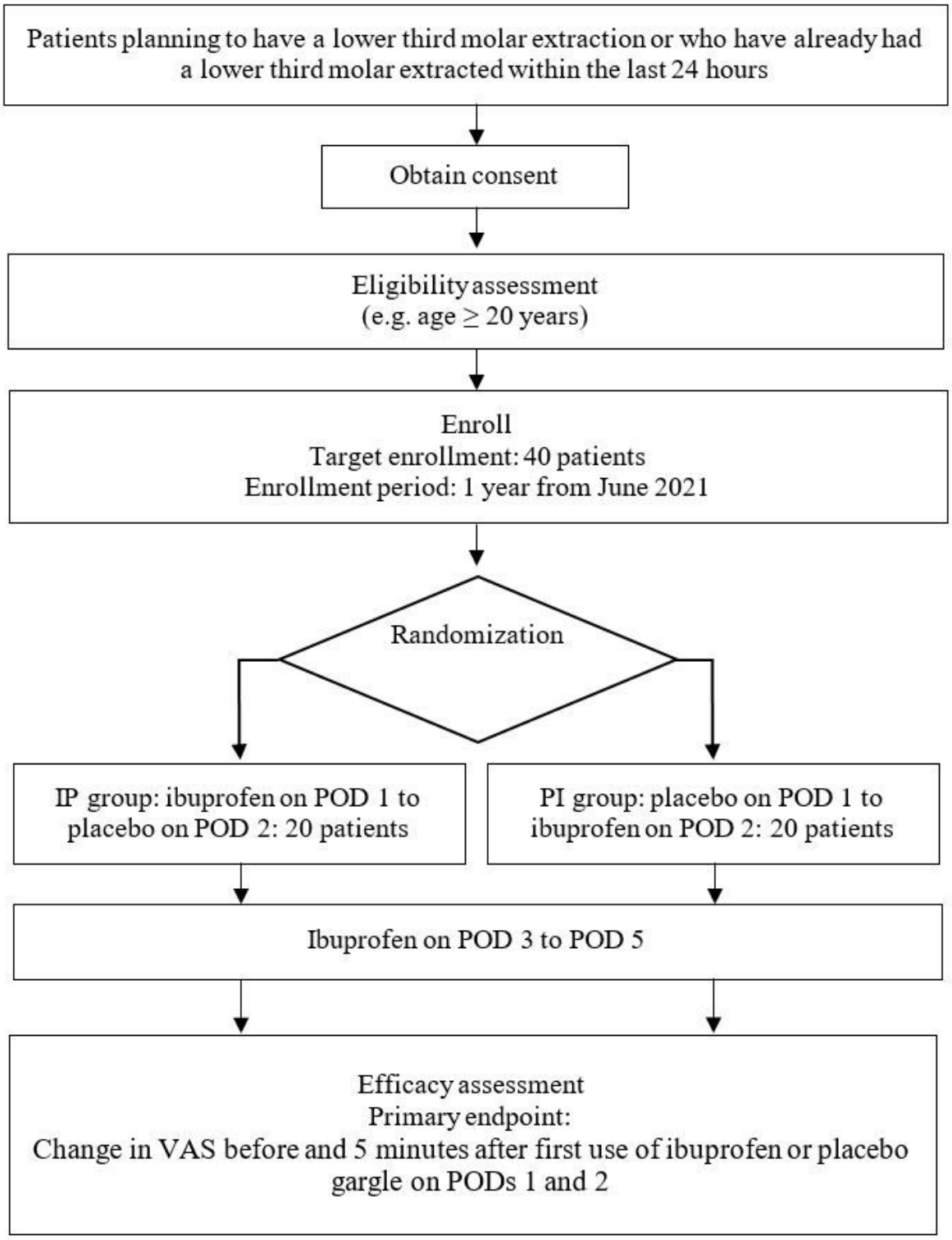

Figure 1

Flowchart of the study design POD: postoperative day VAS: visual analogue scale

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklistIbu.doc