STUDY PROTOCOL, STATISTICAL ANALYSIS PLAN (SAP) AND INFORMED CONSENT FORM (ICF)

Study Title : The Effect of Allopurinol on Malondialdehyde, Nitric Oxide, Kidney Injury Molecule-1 Urine Levels, Resistive Index and Renal Elastography in Kidney Stone Patients After Extra Corporeal Shockwave Lithotripsy

Principal Investigator: Kadek Budi Santosa, MD, Urologist

Urology Department, Sanglah General Hospital

Human Subjects Review Approved Dated : 03.08.2020

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STUDY PROTOCOL

1.1. Study Design and Patient Selection

This study was designed as a randomized, double-blind placebo-controlled trial to assess the effect of allopurinol administration in reducing tubular damage, vascular dysfunction and focal zone biophysical changes in the kidney due to ESWL.

Patients were randomly assigned to the intervention and placebo groups in this clinical study. The study group was formed of patients with kidney stone who undergo ESWL.

1.2. Process and Intervention

Patients with kidney stones who will undergo ESWL were randomized into 2 groups. Group 1 was given allopurinol, and group 2 was given a placebo. Allopurinol 300 mg was administered orally for a total of 3 days, starting from the day before ESWL. Malondialdehyde (MDA), nitric oxide (NO), kidney injury molecule-1 (KIM-1) in urine were measured by technique quantitative double antibody sandwich direct ELISA before ESWL, continued two hours, and 24 hours after ESWL. Changes in the interlobar artery resistive index (RI) were assessed together with measurements of shear wave velocity (SWV) values in the renal focal zone before ESWL, followed by two weeks, and four weeks after ESWL.

1.3. Safety Evaluation

If there was any drug side effects or serious adverse events(SAE), the subjects were reported to the ethics committee as soon as possible, less than 24 hours from the first time they were discovered, and actions were carried out as quickly as possible until the series of events ends. SAE was written in detail on the SAE form, including the following; when it was first discovered, the manifestation of the incident, the conditions before the incident, the handling of the event, and the outcome.

If the subject experiences side effects such as allergic reactions (redness of the skin, swelling of the eyes or mouth) and severe gastrointestinal disturbances (vomiting, diarrhea), the subject will be excluded from the analysis. The subject will also be excluded from the analysis if the subjects experience complications related to ESWL

procedure such as ureteral obstruction, pain (VAS > 5), or there were signs of infection. Subjects will be evaluated when visiting the hospital according to schedule, telephone contact, or by making a home visit.

1.4. Sample Size

The Population of the study consisted of patients with kidney stones who will undergo ESWL. The sample size was calculated based on the statistical diagnosis of the study which is, comparative analysis of independent two groups. A total of 70 subjects were planned to be included in the study, 35 of which were intervention while the rest were placebo. Patients were randomly assigned to both groups in this study.

1.5. Ethical Approval

Approval for the study was granted by the Research Ethics Committee Faculty of Medicine, Udayana University(Number: 1637/UN14.2.2.VII.14/LT/2020). Verbal and written informed consent was obtained from all subjects in the study.

Author Contributions

Conflict of Interests

The Authors have no conflict of interests to declare

Acknowledgements

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Financial Disclosure

STATISTICAL ANALYSIS PLAN (SAP)

Data collected in this study were analysed statistically using SPSS for Windows software 25. Data were analysed by descriptive statistics to describe the characteristics of the subjects based on the treatment group and presented in the form of a distribution table. The compatibility of the variables on the numerical data scale uses the average comparison with the independent t-test. The categorical-scale variables used the proportion comparison with chi-square test. The limit value of significance was set at 0.05. The normality data assessment in this study is based on the central limit theorem, where the sample size in each group more than 30 makes the z distribution close to the t distribution and the data will be normally distributed. Bivariate and Multivariate analyses were performed using repeated measure ANOVA to control covariates. The value of the limit of significance is set to 0.05.

INFORMED CONSENT FORM (ICF)

We are looking forward to your participation in this clinical study that held by dr. Kadek Budi Santosa, Urologist, entitled "The Effect of Allopurinol on Malondialdehyde, Nitric Oxide, Kidney Injury Molecule-1 Urine Levells, Resistive Index and Renal Elastography in Kidney Stone Patients After Extra Corporeal Shockwave Litothrypsi".

You have kidney stones who are going to undergo ESWL, thus were asked to participate in this study. Please read this information prior to determine if you are going to participate or not. Please don't be hesitate to ask if there is something unclear. If you decide to participate in this study, we expect you will follow the instruction given.

This study is held to evaluate if administration of antioxidants, allopurinol, will be able to prevent or reduce kidney damage due to ESWL. Allopurinol itself is already available in the market and both its efficacy and safety have been proven.

This study will include 80 subjects. You will be randomized to two groups. One group will get allopurinol 300mg while the other group will get placebo. Both you and the doctor do not know which drug you get. The drug is given in three capsules, which is consumed one day and one hour prior to ESWL, followed by one day after ESWL. Urine examination will be done one hour prior to ESWL, followed by two hours and one day after ESWL. Ultrasound examintation will be done one hour prior to ESWL, followed by two weeks and one month after ESW.

Allopurinol may give side effects of nausea, vomiting or diarrhea, this drugs may also cause alergy. If those happen, the doctor will stop the medication and hold until you get better.

If any damage due to this study happen, you will be given help and it is free of charge. You will follow health protocol equipped by standard personal protective equipment given by the doctor through the process in the hospital.

This participation is voluntary. You may object to participate or quit anytime of this study. In case you object to participate, you keep getting the treatment according to protocol. The doctor will exclude your participation if the instruction is not followed.

The data collected in this study will be kept anonymously. Only the researcher knows your data. This study result may be published in any scientific forum, health magazine, or international journal without disclosing subject's identity.

The health worker who appointed by government organization will make sure your medical history is confidential and this study is going well. It will be done with your consent and by signing this form, subjects have understood and given the consent.

If subject find any harm in this participation, thus compensation will be discussed between the subject and the person in charge of this study.

Any harms or if there is any question regarding this study, please contact: dr. Kadek Budi Santosa, Urologist at Department of Urology Sanglah Hospital, Cell phone 081339977799 or Sanglah General Hospital (0361) 227912

All the explanation above has been delivered to me and all of my consideration has been answered by the doctor. I understand that I may ask dr. Kadek Budi Santosa, Urologist if I need further explanation.

By signing this form, I give my consent to participate in this study.
Study's Participant/Subject:

……. …….
Date Signature
(Full Name : ……..)

Witness:

……. …….
Date Signature
(Full Name : ……..)

Note:

- Witness' signature is required if the subject is blind or illiterate
- Witness is someone who have legal relationship with subject.