CLINICAL STUDY PROTOCOL

Study Title	: A Clinical Trial of Locally-Made Titanium Miniplate and Screw In Maxillofacial Fractures Management
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INTRODUCTION AND RATIONALE

Maxillofacial trauma is one of the most devastating injuries for all plastic surgeon to face. Many problems occurred following this injury, such as loss of facial function, severe morbidity, high financial cost or even death.1,2,3 Motor vehicle accidents are the one who responsible for the most maxillofacial injuries, besides violence by other people. As many as 50–70% of people who survive traffic accidents have facial trauma4 with a peak incidence occurring between ages 20 and 40 which are productive ages5

Indonesia as one of the developed country in the world, maxillofacial fractures also caused by motor vehicle accidents. Data from several centers in Indonesia show that dr. Soetomo Hospital Surabaya taking care of 160 cases of maxillofacial fractures,6 while, Arifin Achmad Hospital Pekanbaru treated 413 facial trauma cases during 2010-2013. In Cipto Mangunkusumo Hospital Jakarta 494 patients were treated during 2015-2017.

When there are displaced and unstable fracture segments leading to functional disturbance, for example, diplopia and malocclusion, open reduction and internal fixation using miniplate and screws are indicated to achieve the goal of maxillofacial fractures management. This internal fixator creates stability and allows early rehabilitation of the site of the fractures.7,8,9

The miniplate and screw system for maxillofacial fractures that are widely used and available at Cipto Mangunkusumo Hospital are Biomet® and Osteomed®. Both brands are imported and similar in their quality. These brands, however, are very costly due to the importing expenses and luxury goods additional tax. Based on government law number 42, 2009, Chapter 5, imported medical devices are considered as luxury goods and will be charged with selling tax up to a minimum of 10 percent. Moreover, BPJS as national healthcare insurance in Indonesia comes to a serious deficit, therefore they demand the hospital to be more careful on patient management. In our hospital, through a division of "Kendali Mutu Kendali Biaya" (KMKB), they control the application of every medical implant, an expensive drug used and other expensive procedure.

A locally-made miniplate and screw as internal fixators for maxillofacial fracture have been studied before on an animal. Previously conducted animal study the local miniplate and screw did not produce any wound complication with respect of infection, seroma, and hematoma during observation and the bone is healed according to the timeline.33 Moreover, local miniplate and screw fixation allow a not-inferior bone healing compared to import one in terms of bone density, muscle density, and peri-implant bone density.34 Furthermore, this locally-made miniplate and screw needs to face greater force and more complex system in the human body. Therefore, we will use it in patients with maxillofacial fractures, to evaluate the locally-made miniplate and screw efficacy while also reducing the cost that has to expend by our national health insurance.

As stated in The Ministry of Health Regulations number 86, 2003 regarding The Road Map Development of Medical Equipment Industry, Ministry of Health demands local medical products to grow faster. On the contrary, medical devices currently available in Indonesia could not provide the demand for medical products. Ninety percent of medical products that are distributed in Indonesia are imported. In the globalization era, many products enter Indonesia easily, while the supply could not meet the demand, causing the price of these medical products

increases every year. As a result, the need for healthcare service and medical products supply does not meet.10

Also addressing to the new national healthcare system number 27, 2014 regarding Technical Instructions System of Indonesian Case Base Groups, where medical coverage is not based on medical expenses but the grouping of diagnoses and treatment based on ICD-9, the high cost of medical products often complicate the hospital policy.11

Therefore, as suggested by the Indonesian Ministry of Health, we are going to use our local plate and screw for maxillofacial fractures management to answer the balance of supply and demand of local medical products. On the other hand, it could help the government to reduce medical expenses.

Aim Of The Study

The aim of this experiment is to investigate the usage of the locally-made miniplate and screw are not inferior compared to the existing benchmark miniplate and screw in terms of bone healing, surrounding tissue reactions, and screw loosening.

Study Hypothesis

The locally-made miniplate and screw are not-inferior compared to the existing benchmark miniplate and screw in terms of bone healing, surrounding tissue reactions, and screw loosening.

OBJECTIVES AND OUTCOMES

Primary Objective

To evaluate bone density radiologically (in Houndsfield Unit) after plate and screw fixation with locally-made compared to existing benchmark miniplate and screw

Secondary Objective

- To evaluate if there is any loosening screw following both locally-made and existing benchmark miniplate and screw fixation.
- To evaluate if there is any sign of local tissue reaction following both locally- made and existing benchmark miniplate and screw fixation.

STUDY DESCRIPTION

Research Design

This study will be performed on patients with maxillofacial fractures. The study is a blind randomized clinical study comparing locally-made titanium plate and screws with the existing benchmark, BIOMET® miniplate, and screw. After fixation, bone density, local tissue reactions, and screw loosening between these two devices at specific periods will be compared.

Time And Place

The clinical study will be conducted at Cipto Mangunkusumo Hospital, Jakarta, Indonesia from September 2019 – April 2020. Surgery will take place at Cleft Craniofacial Center Operating Theatre. It will be conducted by two consultants of craniomaxillofacial surgeons.

STUDY POPULATION

Inclusion Criteria

- Midface fracture with the indication of surgery
- Midface fracture sustained within 2 weeks

Exclusion Criteria

- Comminuted and defect fracture
- Midface fracture on patients with systemic diseases affecting bone healing.
- Midface fracture in children
- Midface fracture in multiple trauma patients with neurological deterioration

Dropout Criteria

- Patient who is unable to complete radiological evaluation after surgery due to lost to follow up or refuse to continue the evaluation will be replaced by another sample
- Patient with signs of bacterial infection either locally or systemically or implant failure are not dropouts, their last data of observation will be included and analyzed (Last-Observation-Carried-Forward (LOCF) method).

METHODOLOGY

Subject Allocation

Subject is the fracture line found on the patient. The surgeon is not blinded on which miniplate is going to use because the miniplate has different characteristic.

Intervention

Pre-operatively

- Patients will sign the informed consent sheet and declare that they want to be enrolled as subjects and obey all the instructions given postoperatively
- The patients will shower with chlorhexidine 4% 27 soap 1 day before surgery
- An empiric antibiotic will be administered 1 hour preoperatively: intravenous injection of Ampicillin Sulbactam 1.5 gr/IV 28 to prevent postoperative infection.

Intra-operatively

- All patients will be treated under general anesthesia.
- After induction of anesthesia, the operating field is disinfected with povidone-iodine
- Draping the patient, exposing only the area of surgery
- Local anesthetic solution with a vasoconstrictor is administered along the incision line area for homeostasis
- Maxillary mandibular fixation is performed to maintain the occlusion
- Midface fracture site approach through an intra-oral or extra-oral incision according to the accessibility at that time and may differ for every patient
- The fractured segment is reduced into proper position using Carrol-Girrard, hook, elevator or Rowe disimpaction forceps.

- The surgeon will received a seal envelope contain an instruction to use locally-made miniplate or existing benchmark miniplate and then it will be bend as desired based on the fracture site contour
- The surgeon will place the miniplate on the fracture site based on AO/CMF point fixation sequence.
- The plate is tapped manually with gentle pressure. The screw is inserted into the hole using a screwdriver and held parallel to the long axis of the drill hole.
- The steps of drilling, tapping and screwing all panel holes are repeated for all screw holes followed by the closure of the incision with usual manner.
- The maxillary mandibular fixation is removed and the jaw is manipulated to evaluate the occlusion and also measure the maximal mouth opening. Forced-duction test is performed when there is a placement of the plate on the orbital rim.
- The maxillary mandibular fixation is maintained for approximately 2 weeks and evaluates once a week during patient visit to the outpatient clinic

Post-operatively

- Intravenous injection of Ampicillin Sulbactam 1.5 gr every 6 hours is given for 1-2 days, then when the patient is discharged it is replaced by Amoxicillin/clavulanic acid 625 mg orally every 8 hours for another 7 days post-operatively
- Intravenous injection of Paracetamol 1 gr every 8 hours is given for 2 days followed by oral tablets 500 mg every 8 hours as needed for another 7 days for pain control
- All patients undergo a non-contrast head CT scan on day one postop as a baseline
- All patients are discharged two days after surgery and instructed to have liquid diet for 2 weeks post-operatively
- Patients will visit the outpatient clinic once a week for 3 weeks. Sign of bacterial infection or local tissue reaction will evaluate by the end of 3rd week
- All patients performed a non-contrast head CT scan at 3 months postoperatively.

Miniplate And Screw Placement

Once a patient lies down on the operating table under general anesthesia, the surgeon will identify the fracture segment. The surgeon will received a seal envelope contain an instruction to use locally-made miniplate or existing benchmark miniplate to be placed on the fracture site according to a predetermined randomization list. The decision where to place the locally made miniplate or existing benchmark miniplate depends on AO/CMF point of fixation sequence.

Assessing Study Results

After completing the procedure, subjects will undergo non-contrast head CT scan evaluation immediately after surgery as a baseline, and by the end of 3rd months post-operation. Afterward, a radiologist consultant as a blinded independent evaluator will assess the bone density score in each subject. A score sheet will be given to the assessor. Subjects will also be instructed to visit the outpatient clinic once a week for 3 weeks post-operatively to evaluate their appearances clinically if there is any sign of bacterial infection or local tissue reaction that will be taken care of by consultants of craniomaxillofacial surgeons.

Bone Density

Bone density of each subject will be recorded in Hounsfield Unit (HU). The bone density score of each subject will be noted and scores between the two brands will be compared. The scores will be evaluated by a radiologist consultant and act as an independent evaluator after the subject has completed all their Head CT evaluation.[29, 30]

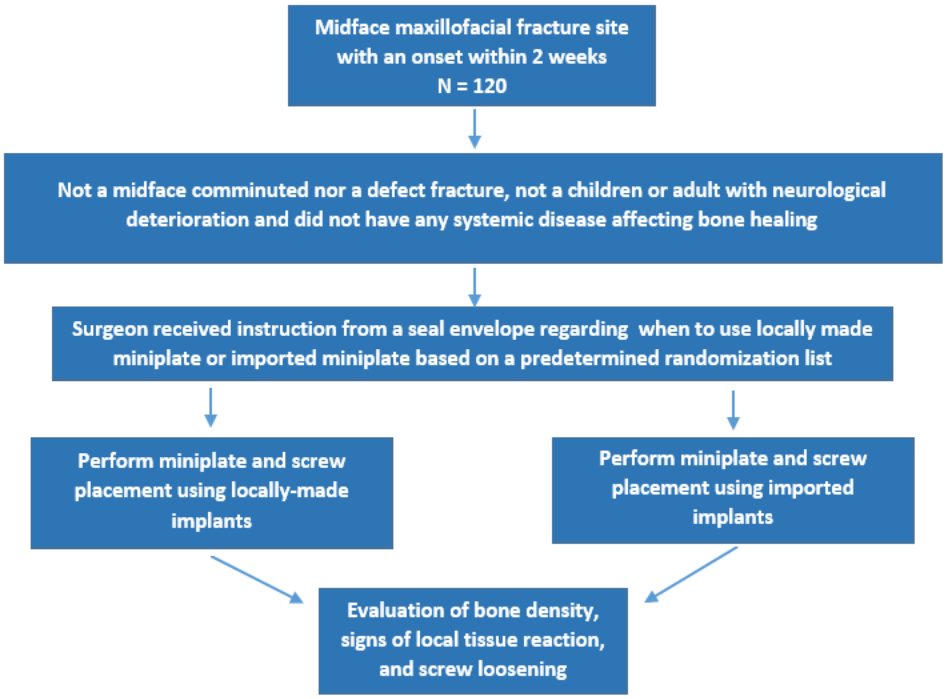
Screw Loosening

Screw loosening will be recorded, whether it is present or not. It will be evaluated by a radiologist consultant after the subject completed all their Head CT evaluation.

Tissue reaction

Local tissue reactions such as edema, bacterial infection, or any other signs of the inflammation process, will be recorded by the end of the 3rd week during patient's visit outpatient clinic. It will be evaluated by consultants of craniomaxillofacial surgeons and.

Research Protocol



DATA ANALYSIS AND DATA PRESENTATION

Data on bone density are quantitative, all scores from points of evaluation group will be collected, and scores for the dependent variables between groups will be statistically compared using independent t-test or Mann Whitney test depending on the distribution of the data is normal or not. Other findings will be presented using descriptive statistics.

Table 2. Dummy table of bone density (HU) in group I (Locally-made miniplate and screw) versus group II (existing benchmark miniplate and screw) at different observation periods.

Time (Postop)	Group I (Mean ±SD)	Group II (Mean ±SD)	p-Value*
Bone Density			
Immediately post op			
Three months post op			

*Statistically significant difference versus baseline reading if p-value ≤ 0.05 HU=Hounsfield unit.

Table 3. Dummy table of local tissue reaction and screw loosening presence in group I (Locally-made miniplate and screw) versus group II (existing benchmark miniplate and screw) at different observation periods.

Time (Postop)	**Group I (n=60)**	**Group II (n=60)**
Local tissue reaction presence		
3rd week		
Screw loosening presence		
Immediate post op		
2 months post op		

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