A Prospective Double-Blinded Randomized Controlled Trial of The Efficacy of Haruan (*Channa striatus*) Spray on Clean Wounds.

DR. NIK AMIN SAHID BIN NIK LAH

Dissertation Submitted In Partial Fulfillment of The Requirements For
The Degree of Master of Medicine
(General Surgery)

UNIVERSITI SAINS MALAYSIA
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ACKNOWLEDGEMENTS

An endless thanks to Allah the Almighty

I would like to express my special appreciation to my supervisors, Dr Rosnelifaizur bin Ramely and Dr Ikhwan Sani Mohamad. Dr Syed Hassan Bin Syed Abd Aziz, Dr Arman Zaharil Mat Saad, Prof Ahmad Sukari Halim, Dr Mohd Nizam Md Hasim as a co-investigator, for their expert opinion, dedicated help, guidance and comments throughout the research project and subsequent writing up of this dissertation.

Special thanks to Dr Najib Majdi Yaacob from Unit of Biostatistics and Research Methodology of School of Medical Sciences for statistical assistance.

Last but not least, my beloved parents (Nik Lah Said and Saleha Mat Saud), my wife Nazimah Masor and my lovely son and daughter Nik Harith Eyrfan and Nik Adriana Aleesya for always supporting me in completing this thesis.

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ABSTRAK

Latar belakang

Berdasarkan kepada banyak kajian-kajian yang dijalankan sebelum ini mendapati bahawa *Channa Striatus* (Ikan Haruan) dapat membantu mempercepatkan proses penyembuhan luka dan juga mampu mengurangkan tahap kesakitan pada luka. Walau bagaimana pun, setakat ini kajian-kajian ini hanyalah dijalankan terhadap haiwan . Masih belum terdapat kajian yang khusus tentang kesan Channa Striatus (Ikan Haruan) terhadap kualiti penyembuhan luka dari segi kosmetik dan pengawalan tahap kesakitan kepada manusia. Jadi, satu kajian prospektif tentang kesan semburan ekstrak ikan Haruan terhadap luka pembedahan bersih di jalankan.

Metodologi

Seramai 102 orang yang menjalani pembedahan elektif yang dikategorikan bersih telah dirawakkan kepada dua kumpulan A dan B . Kumpulan A menerima semburan ikan haruan terhadap luka pembedahannya (n=51) manakala kumpulan B menerima semburan placebo (n=51). Semua luka pesakit di nilai pada minggu ke 2, 4 dan 6 dari segi kosmetik berdasarkan 3 sistem pemarkahan iaitu VACS (Visual Analogue Cosmetic Scale),WES (Wound Evaluation Scale),VSS (Vancouver Scar Scale). Tahap kesakitan pada luka pembedahan turut dinilai berdasarkan kepada system pemarkahan VAPS (Visual Analogue Pain Score).

Keputusan

Daripada 102 pesakit, seramai 21 orang pesakit telah tercicir daripada kajian kerana tidak dapat menghadiri temujani susulan. Analisis terhadap 81 pesakit menggunakan kaedah ‘Repeated measure ANOVA didapati bahawa tahap kesakikatan menggunakan VAPS adalah lebih baik bagi pesakit yang menerima ekstrak haruan berbanding pesakit yang menerima placebo. RM Anova: (F-stat(df) = 4.80 (2), p-value = 0.010). Analisa bagi pesakit yang mendapat rawatan semburan pati ekstrak ikan haruan turut menunjukkan kesan kosmetik yang lebih baik berdasarkan system VACS, (F-stat(df) = 2.68 (2) , p-value <0.001), WES (F-stat(df) = 3.09 (2), p-value = 0.048) and VSS , F-stat(df) = 1.72 (2) , p-value = 0.011).

Kesimpulan

Hasil kajian mendapati bahawa luka bersih yang di rawat dengan semburan ekstrak haruan adalah lebih baik berbanding dengan placebo dari segi kosmetik dan tahap kesakitan pada minggu ke 2, ke 4 dan minggu ke 6.

ABSTRACT

Background

Channa striatus (Haruan), a fresh water fish indigenous to many tropical countries have long been regarded as valuable food fish in the Far East. Several studies showed, the Haruan did contain all the essential amino acids and fatty acids uniquely capable of accelerating the wound healing and it has anti-nociceptive effect. However so far no human study been done to assess the effectiveness of *Channa striatus* in wound healing. A prospective randomize controlled trial has been conducted on the effect of *Channa striatus* Spray versus placebo on clean wound to assess its pain control effect and cosmetic outcome.

Methodology

Hundred and two patients (102) underwent clean elective surgery; post-operatively they are randomized into two group. One group received *Channa striatus* Extract spray (n=51) another group receive placebo (n=51) on daily basis for 2 week. Then they were follow up on 2^{nd}, 4^{th} and 6^{th} week to assess the pain control effect based on Visual Analog Pain Score (VAPS) and cosmetic outcome based on Visual Analogue Cosmetic Scale (VACS), Wound Evaluation Scale(WES) and Vancouver Scar Scale (VSS).

Result

The patient treated with *Channa striatus* spray displayed a better outcome in term of pain control compared to placebo. During analysis using repeated measure ANOVA, there was significant difference of patient's pain score based on VAPS between *Channa striatus* spray and placebo (F-stat(df) = 4.80 (2), p-value = 0.010). In term of cosmetic outcome it showed a consistent significant better result in haruan spray group for all the 3 scoring system which is VACS, (F-stat(df) = 2.68 (2) , p-value <0.001), WES (F-stat(df) = 3.09 (2), p-value = 0.048). and VSS , F-stat(df) = 1.72 (2) , p-value = 0.011).

Conclusion

Our study suggest that application of Haruan Extract spray on clean wound has shown a significant better pain score result and cosmetic outcome on week 2, week 4 and week 6 comparatively with placebo.

1.0 INTRODUCTION

1.1 Introduction

Channa striatus (Haruan), a fresh water fish indigenous to many tropical countries have long been regarded as valuable food fish in the Far East. Their flesh is claimed to be rejuvenating, particularly in recuperation from serious illness and in a post-natal diet. In Malaysia, it has always be a strong belief that *Channa striatus* enhance wound healing and a very powerful tool for recovery of health and injury. Since 1931 there has been in Malaysian literature discussing about wound treatment using *Channa striatus.* Several studies showed that it contained all the essential amino acids and fatty acids which uniquely capable of accelerating the wound healing (1, 2).

Despite the wide-spread uses of this fish for medicinal purposes, there have been hardly any studies to establish the scientific basis for its claimed wound healing effects. In an animal study, *Channa striatus* extract has shown to increase the tensile strength of the surgically stitched wound. It also has been formulated into aerosol/spray for drug delivery system to wound and burn treatment (3, 4). Evaluation of the film properties from concentrate of aerosol had been done in other study (5). But the effect on human has not been done yet. Therefore the effects of *Channa striatus* extract in aerosol form on clean surgical wounds are evaluated in this study.

1.2 Literature review

1.1) Definition of wound

Wound is defined as a breakdown in the protective function of the skin; the loss of continuity of epithelium, with or without loss of underlying connective tissue following injury to skin or underlying tissue or organ caused by surgery, a blow, a cut, chemicals, heat, friction, pressure or as a result of a disease. i.e. carcinoma, leg ulcer.

1.2) Wound classification

Wound can be classify based on (6-8)

a) Etiology (e.g. : surgical,crush injury,)
b) Morphology (e.g. : degloving, laceration, abrasion)
c) Contamination (e.g. : clean, clean-contaminated, contaminated or dirty)
d) Complexity (e.g. : simple, complex, complicated)
e) Thickness (e.g. : superficial, partial thickness, full thickness)

1.3) Wound healing process

In healing process, wounds are either closed by primary intention or delayed primary closure. It also can left to heal by secondary intention.(9, 10). Wound healing is a dynamic process which can be divide into three phases. It is critical to remember that wound healing is not linear and often wounds can progress both forwards and back through the phases depending upon intrinsic and extrinsic factor within the patient(11, 12)

The phases of wound healing are (13) :

- Inflammatory phase
- Proliferation phase
- Maturation phase

The **inflammatory phase** is the body's natural response to injury. After initial wounding, the blood vessels in the wound bed contract and a clot is formed. Once haemostasis has been achieved, blood vessels then dilate to allow essential cells; antibodies, white blood cells, growth factors, enzymes and nutrients to reach the wounded area. This leads to a rise in exudate levels so the surrounding skin needs to be monitored for signs of maceration. It is at this stage that the characteristic signs of inflammation can be seen; erythema, heat, oedema, pain and functional disturbance. The predominant cells at work here are the phagocytic cells; 'neutrophils and macrophages'; mounting a host response and autolyzing any devitalized 'necrotic / sloughy' tissue.

During **proliferation**, the wound is 'rebuilt' with new granulation tissue which is comprised of collagen and extracellular matrix and into which a new network of blood vessels develop, a process known as 'angiogenesis'. Healthy granulation tissue is dependent upon the fibroblast receiving sufficient levels of oxygen and nutrients supplied by the blood vessels. Healthy granulation tissue is granular and uneven in texture; it does not bleed easily and is pink / red in colour. The colour and condition of the granulation tissue is often an indicator of how the

wound is healing. Dark granulation tissue can be indicative of poor perfusion, ischaemia and / or infection. Epithelial cells finally resurface the wound, a process known as ‘epithelialization’.

Maturation is the final phase and occurs once the wound has closed. This phase involves remodeling of collagen from type III to type I. Cellular activity reduces and the number of blood vessels in the wounded area regress and decrease.

1.4) *Channa Striatus* (Haruan)

Figure 1: *Channa striatus* (Haruan Fish)

Channa Striatus is a fresh water species which also knows as snake head fish or known as Haruan in Malay. It is indigenous species to many tropical countries such as India, Thailand, Malaysia, and Indonesia. It belongs to Channidea family and it is carnivorous fish.

1.5) Traditional believe on *Channa striatus*

Traditionally Malay and Chinese community believe eating *Channa striatus* during postpartum period has a good effect on the post-delivery wound. It also believe that *Channa striatus* act as energy booster meal. A study done among Chinese respondents in a Kuala Lumpur maternity hospital involved questions on the consumption of *Channa striatus*.(14)

1.6) Nutrition composition of *Channa striatus*

Study found that *Channa Striatus* extract to have rich in amino acids, a nonessential amino acid which glutamic acids arginine and aspartic acid (15) .Others were listed in the table below.

Table 1. Composition of amino acids and fatty acid in *Channa striatus* extract

	Fillet	**Roe**	**Mucus**
Amino acids	**Glycine** **Glutamic acid** **Arginine** **Aspartic acid**	**(No study)**	**(No study)**
Fatty acids	Eicosapentaenoic Acid (EPA) Docosahexaenoic Acid (DHA) Palmitic acid Oleic acid Stearic acid Arachidonic acid	Eicosapentaenoic Acid (EPA) Docosahexaenoic Acid (DHA) Hexadecanoid acid Oleic acid Linoleic acid	Oleic acid Linoleic acid

Adopted from (16)

1.7) Composition of Channa striatus spray

Haruan water extract has been formulated in an aerosol system which can produce a film for wound dressing. It was manufactured by Skin Fix Company. Haruan spray has been evaluated for the possibility to cause irritation reaction or toxic response however from three experiments were carried out to evaluate the safety of Haruan spray which are Primary Skin Irritation test, Intracutaneous test and Systemic Injection test, the result shows that Haruan spray gave no significant responses to all the above tests (17, 18). In 2011, Febriyenti have formulated an aerosol concentrate containing a mixture of haruan extract and a film-forming polymer. The concentrate when sprayed on the wound formed a thin layer of dressing and the added haruan extract proved to enhanced the healing process as proven by Baie and Sheikh studied the wound healing effect of C. striatus in Sprague-Dawley rats (19).

1.8) *Channa striatus* in as anti-microbial

As a part of the wound healing process, antimicrobial activity is equally important. The antimicrobial properties of the skin and intestinal mucus of different *Channa sp. viz: C. striatus, Channa micropeltes, Channa marulius, Channa punctatus* and *Channa gachua* have been studied by CARE research team. The investigation showed a broad spectrum of antibacterial activity of skin mucus against Aeromonas hydrophila ,Pseudomonas aeruginosa and Vibrio anguillarum.(20)

1.9) Antinociceptive properties Haruan

The analgesic or antinociceptive effect were being studied by a few researchers. For instance, Mat Jais et al (1997) investigated the antinociceptive effects in mice with a view to establishing the scientific basis of pain-relieving activities where the study showed that both the fillet and mucus of *Channa striatus* were found to exhibit a concentration dependent antinociceptive activity (21). There are evidences for arachidonic acid of haruan enhancing the activity of other antinociceptive agents such as morphine (21).

1.3 Rationale of Study

Clean surgery procedure is one of major bulk of general surgery work load. It occupy almost 40% of all elective case. Post-operative pain and cosmetic outcome is one of major concern for the patient and potentially debilitating. Previous animal study has proven that haruan extract has improved tissue healing. However there is no human study done regarding the effect of haruan spray on cosmetic outcome and pain contral. It is clinically useful if we can identify the effectiveness of haruan extract spray on clean wound, which can be potentially extend to clean contaminated wound in future.

2-STUDY PROTOCOL

2.1- DOCUMENT SUBMITED FOR ETHICAL APPROVAL

A Prospective Double-Blinded Randomized Controlled Trial of the Efficacy of Haruan (*Channa striatus*) Spray on Wounds.

Background/Introduction

In Malaysia, it has always be a strong belief that Haruan enhances wound healing and act as a very powerful tool for recovery of health and injury. Since 1931 there has been in Malaysian literature talking about wound treatment using Haruan. Several studies have been carried out to examine the efficacy and contents of Haruan meat. Indeed, the Haruan did contain all the essential amino acids and fatty acids uniquely capable of accelerating the wound healing.

Channa striatus (Haruan), a fresh water fish indigenous to many tropical countries have long been regarded as valuable food fish in the Far East. Their flesh is claimed to be rejuvenating, particularly in recuperation from serious illness and in a post-natal diet. It is consumed for its putative effects on wound healing (22, 23). It is also used by the patients in the post-operative period in the belief that it promotes wound healing and reduces post-operative pain and discomfort. This fish is known to contain polyunsaturated fatty acids that can regulate prostaglandin synthesis and hence induce wound healing (24). Certain amino acids like glycine, aspartic and glutamic acid are also known to play important roles in the process of wound healing (25-27).

Despite the wide-spread uses of this fish for medicinal purposes, there have been hardly any studies to establish the scientific basis for its claimed wound healing effects. Previously (22) reported that the fatty acid composition of Haruan may account for the promotion of wound healing process. Gam et al. (28) reported that there are no significant differences in the content of amino acid and fatty acid compositions in this snakehead fish of various sizes and obtained at different times of the year (29).

Cream extracts of Haruan tissues contain high levels of arachidonic acid, a precursor of prostaglandin, essential amino acids (particularly glycine) and polyunsaturated fatty acids necessary to promote prostaglandin synthesis. Treating wounds with these extracts has been demonstrated to promote synthesis of collagen fibers better than standard use of Cetrimide, an antimicrobial quaternary ammonium compound. In that study, Haruan extract was shown to increasing the tensile strength of the surgically stitched wounds when compared to the those treated with Cetrimide cream (30).

Haruan extract have also been formulated into aerosol/spray for drug delivery system to wound and burn treatment (3, 4). Evaluation of the film properties from concentrate of aerosol had been done in other study (5). But the effect on human has not been done yet. Therefore the effect of Haruan extract in aerosol form for incision/surgery wounds will be evaluated in this study.

Objectives of Study

Main Objectives

1) To evaluate the effectiveness of Channa Striatus (Haruan) extract spray versus placebo in term of healing process and wound aesthetic appearance on clean surgical wounds

Specific Objectives

1) To compare the effect of Haruan spray on patient's pain score based on Visual Analogue Pain Score (VAPS).

2) To compare the difference between Channa Stiatus extract spray and placebo in term of cosmetic outmoce based on Visual Analogue Cosmetic Scale (VACS) and Wound Evaluation Scale (WES).

3) To evaluate the resultant scars based on Vancouver Scar Scale (VSS).

Research Methodology

Study Subject/Source Population

This is a randomized, prospective, clinical study to evaluate the effect of topical administered Haruan (*Channa striatus)* extract in aerosol/spray form with the effect of placebo (spray without Haruan extract). Subjects will be recruited from clinic of General Surgery (SOPD), Universiti Sains Malaysia (convenience based sampling). These patient are scheduled for an elective operation with clean incisional wound that are primarily sutured, are subjected to face to face interview to enquire about their suitability of the study. Eligible subjects consenting to participate will be randomly assigned to one of the two groups:

GROUP 1: Subjects receiving Haruan spray

GROUP 2: Subjects receiving placebo spray

Subject must fulfill each of the following criteria for inclusion into this study.

a. Age ≥ 18 and ≤ 50 years
b. Subject who has given written informed consent to participate in the study and understand the nature of the study

Exclusion Criteria

a. Taking any form of herbal extract in the last 3 months before study entry and during the study period
b. History of drug or alcohol abuse.
c. Patient taking warfarin or heparin
d. Clinical relevant cardiovascular, gastrointestinal, hepatic, neurologic, endocrine, haematologic, connective tissue disease or other major systemic diseases that would influence the interpretation of results
e. Patients with medical disorder requiring steroid or immunosuppressive therapy with delay wound healing
f. Patient with chronic cough or other condition which may cause a rise in intra-abdominal pressure
g. Presence of any congenital anterior abdominal wall defects.
h. Patient with evidence of secondary infection post treatment.
i. Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study.
j. Evidence of uncooperative attitude, including poor compliance including inability to attend follow-up visit.

Method of assigning subjects to treatment and placebo groups

Subject eligibility will be established before treatment randomization. Subject number will be allocated strictly sequentially, as subjects are eligible for randomization. A randomization method is by using randomization software at www.randomization.com. Number that has been choosen by the software will determine either the patient will get treatment A or treatment B. None of the investigators will know the randomization scheme.

Blinding and procedures for breaking the blind

This is double blinded study and once a subject has been randomized, the study treatment that they will receive will not be known by both the subject and the investigator.

Patient's withdrawal

The investigator may cease study treatment and withdrew the subject or the subject may withdraw herself from participation in the study at any time. The reason for the withdrawal of a patient will be recorded in the CRF. Subject will be followed-up for a minimum of 42 days (6 weeks) following the last dose of study drug.

Possible reasons for patient withdrawal include:

a. The need to take medication, which may interfere with study measurements.
b. Patient experiences an intolerable / unacceptable adverse event
c. Patient exhibits non-compliance with the protocol
d. Patient unwilling to proceed and / or consent is withdrawn
e. Investigator withdraws patient for reasons unrelated to the study drug (e.g. undercurrent illness)

Investigational products

The topical administered Haruan spray and placebo (spray without Haruan extract) will be prepared in GMP Laboratory, School of Pharmacy Universiti Sains Malaysia.

Doses and treatment regimens

The treatment group will be sprayed with Haruan spray once a day while the placebo group will be sprayed with placebo spray (spray without Haruan extract) once a day.

Data Collection Procedure

Basic demographic data will be collected from the patient and surgical procedure, indication and method of wound closure will be gathered. The wound assessment will be performed by clinical assessment using Visual Analogue Cosmetic Scale (VACS) and Wound Evaluation Scale (WES) by the investigators and also by the patient using Visual Analogue Pain Score (VAPS).

A photo of the wound will be taken serially at every visit and assess by two independent investigators using VACS and WES.

Haruan spray or placebo spray will be used to protect the wound after post-operative wound inspection. All subjects will be instructed to take normal diet during the study period and will not be allowed to take any other herbal products orally or consumed *C. striatus*.

The cosmetic assessments of the wound will be done by the investigator who is part of the Clinical Trial Team. It will be done on week 2, week 4 and week 6 post operations. Subjects will be thoroughly examined by Medical specialists or Medical officers who are part of the Clinical Trial Team at every visit.

Sample Size Determination

The sample sizes are calculated based on two means formula,(using G Power software) the power of the study taken at 90% and alpha (type one error) as 0.5%. The calculations are based on previous study (2, 31) .

Power	= 90%
Type 1 error (α)	= 0.5%
SD	= 14mm
Expected detectable of mean difference between group	= 10mm
The sample size required for both study limb	= 92
Assuming 10% dropped out rate,	= 10
Total number participants required for the study	= 102

Computer calculation

F tests - ANOVA: Repeated measures, between factors

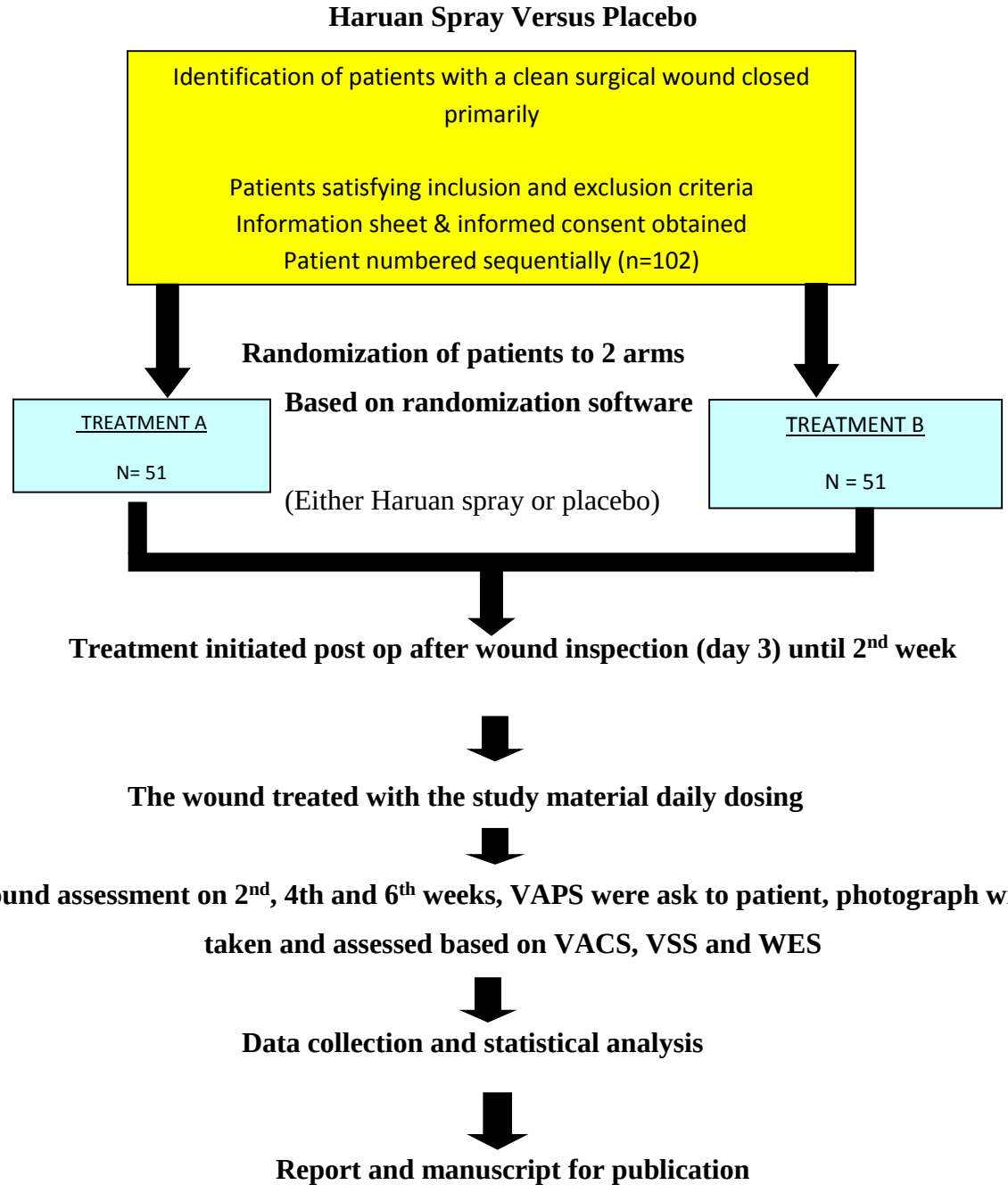
Analysis:	A priori: Compute required sample size		
Input:	Effect size f	=	0.25
	α err prob	=	0.05
	Power (1-β err prob)	=	0.90
	Number of groups	=	2
	Repetitions	=	3
	Corr among rep measures	=	0.3
Output:	Noncentrality parameter λ	=	10.781250
	Critical F	=	3.946876
	Numerator df	=	1.000000
	Denominator df	=	90.000000
	Total sample size	=	**92**
	Actual power	=	0.901176

Expected results table

Table 2: Comparison of mean of the wound aesthetic appearance using VAC Scale among different treatment groups based on time

Time	Treatment group	Mean VAC scale	95% CI
Week 2	**Haruan**	**3**	**2,4**
	Control	**7**	**6,8**
Week 4	**Haruan**	**2**	**1,3**
	Control	**5**	**4,6**
Week 6	**Haruan**	**1**	**1,**
	Control	**4**	**2,4**

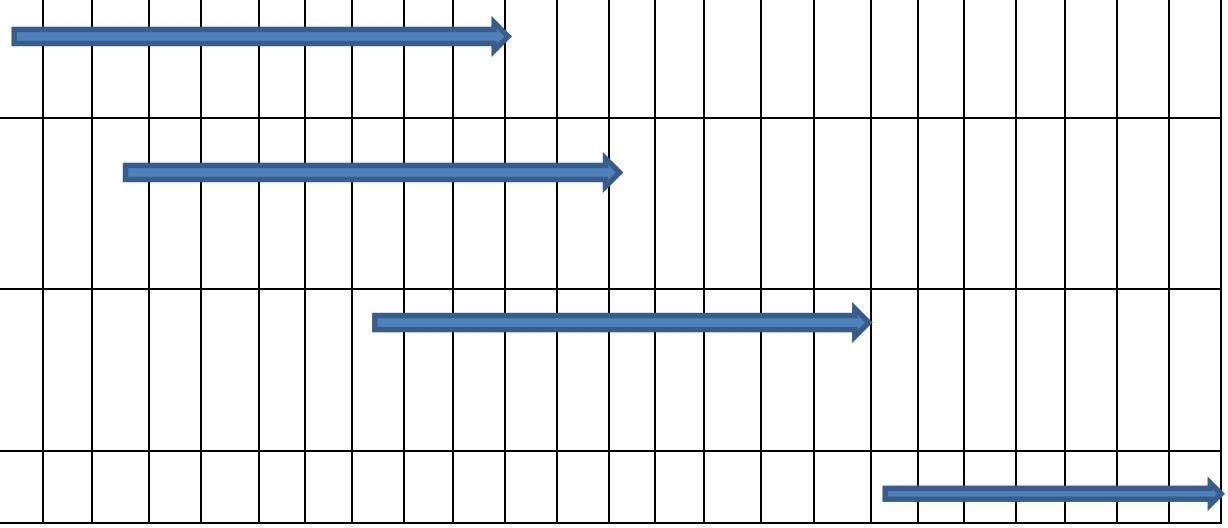
Flow Chart


Haruan Spray Versus Placebo
Identification of patients with a clean surgical wound closed primarily
Patients satisfying inclusion and exclusion criteria
Information sheet & informed consent obtained
Patient numbered sequentially (n=102)
Randomization of patients to 2 arms
Based on randomization software
TREATMENT A
N= 51
(Either Haruan spray or placebo)
TREATMENT B
N = 51
Treatment initiated post op after wound inspection (day 3) until 2nd week
The wound treated with the study material daily dosing
Wound assessment on 2nd, 4th and 6th weeks, VAPS were ask to patient, photograph will be taken and assessed based on VACS, VSS and WES
Data collection and statistical analysis
Report and manuscript for publication

Privacy and Confidentiality.

Privacy and the confidentiality of the data will be protected. Data collected will be stored in hard copy and will only be accessible to the research team. Identifying information will be kept by researcher during the data collection phase for tracking purposes only.

		2015												2016											
No	Activity	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
1.	Subject recruitment and dispensing of medication																								
2.	Follow up/ questionnaires, wound investigations																								
3.	Data analysis																								
4.	Report and publication																								



Gannt Chart

Milestone

6 month (June 2015): 60 % subject has been recruited, 25 % completed the wound investigation
12 month (Dec 2015) : 100% subject has been recruited and completed the wound investigation
18 month (June 2016) : Completed the data analysis
24 month (Dec 2016) : Completed the project report and publication.

Performa

Patient Study Number:

Age:

Gender: M/F

Race:M/C/I/others

Type of surgery: Hernioplasty/Exision Biopsy/Others

Location: neck/chest/abdomen/inguinal

Length of wound: mm

Wound Complication:Heal/infected/dehiscence

Visual Analogue Pain Score (VAPS)

Poor 0 _____ 10 Excellent

/10

Week	Week2	Week 4	Week 6
Score			

Visual Analogue Cosmetic Scale (VACS)

Poor 0 _____ 10 Excellent

/10

Week	Week2	Week 4	Week 6
Score			

Vancouver Scar Scale

Pigmentation	Vascularity	Pliability	Height
0 Normal	0 Normal	0 Normal	0 Normal
1 Hypopigmentation	1 Pink	1 Supple	1 <2mm
2 Hyperpigmentation	2 pink to red	2 Yielding	2 2-5mm
	3 Red	3 Firm	3 >5mm
	4 Red to purple	4 Banding	
	5 Purple	5 Contracture	

/13

Week	Week2	Week 4	Week 6
Score			

Wound Assessment Scale

	At 2 weeks*	At 4 weeks*	At 6 weeks*
Stepoff border			
Contour irregularity-puckering			
Scar width –greater than 2 mm			
Edge inversion-sinking,curling			
Inflammation –redness, discharge			
Overall cosmesis			
Total score			

/6

ASSESSOR NAME : _____

2.2 ETHICAL APPROVAL LETTER

UNIVERSITI SAINS MALAYSIA

Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

Universiti Sains Malaysia
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16150 Kubang Kerian,
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25th February 2015

Dr. Rosnelifaizur Ramely
Department of Surgery
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/1403124
Protocol Title : A Prospective Double-Blinded Randomized Controlled Trial of the Efficacy of Haruan (Channa Striatus) Spray on Wounds.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/1403124**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **March 2015** until **February 2016.**

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Patient Information Sheet and Consent Form (English version)
2. Patient Information Sheet and Consent Form (Malay version)

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Progress report using the **JEPeM-USM FORM 3(B) 2014: Continuing Review Application Form** every 1 year from date of approval (NOTE: In view of active ethical clearance, this report is mandatory even if the study has not started or is still awaiting release of funds.)
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2014: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A)2014: Study Protocol Amendment Submission Form.**
4. Reports of adverse events (if any) including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2014: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2014.**
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2014: Final Report Form.**

9. Application for renewal of ethical clearance 90 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2014: Continuing Review Application Form.**

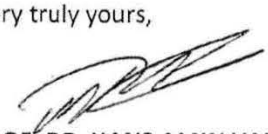
Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

Very truly yours,



PROF. DR. HANS AMIN VAN ROSTENBERGHE
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

3- BODY CONTENT

3.1- TITLE PAGE

A Prospective Double-Blinded Randomized Controlled Trial of The Efficacy of Haruan (*Channa striatus*) Spray on Clean Wounds.

DR. NIK AMIN SAHID BIN NIK LAH

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