Rationale and design for the Shea lubricant, 2% Lidocaine gel non-inferiority trial

Kekeli Kodjo Adanu (kkadanu@uhas.edu.gh)
University of Health and Allied Sciences https://orcid.org/0000-0003-2233-0150
Kokou Amegan-Aho
University of Health and Allied Sciences
Davidson Iroko
University of Health and Allied Sciences
David Adedia
University of Health and Allied Sciences
Orish Verner Ndudiri
University of Health and Allied Sciences

Method Article

Keywords: Shea lubricant, 2% Lidocaine gel, non-inferiority trial, digital rectal examination, pain perception

Posted Date: August 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1972129/v1

Abstract

Introduction: Medical lubricants are indispensable in the care process. Several products are used as lubricants in the medical industry including lidocaine gel. However in Ghana, procurement delays and high cost means the product is not always available. Physicians therefore resort to the usage of inappropriate materials with attendant complications. Shea butter which is locally produced and widely available, when adequately processed may serve as a non-inferior substitute. However data on its use as a medical lubricant is lacking

Objective: To compare the effectiveness, complications and ease of use of shea butter to 2lidocaine gel as a surgical lubricant for digital rectal examination.

Outcomes:

Primary outcome: the primary end point is mean difference in pain perception with a non-inferiority limit set at − 0.72.

Secondary outcome: differences in complication rates including discomfort, urinary urgency, bowel urgency and perianal pruritus. The ease of use and lubricating associated with the use of the lubricant will also be assessed.

Methods: This is a randomized controlled non-inferiority trial comparing the effectiveness of shea lubricant to lidocaine gel for digital rectal examination. A total of 152 patients will be randomized. The data will be collected at the Surgical, Urology and Emergency units of the Ho Teaching Hospital. The study will estimate the differences in pain perception using the Visual Analogue Scale (VAS) with a non-inferiority limit set at − 0.72. The ease of use of the lubricants will be assessed using a Likert scale. Similarly, associated complications such as discomfort, urinary urgency, bowel urgency and perianal pruritus will be ascertained using Likert scales.

Discussion: Lidocaine gels are essential but expensive lubricants. The cost of 2% Lidocaine gel has been estimated to be at least three times that of plain gel in some jurisdictions. Significant cost savings could be made if the Shea lubricant can be substituted for the 2% Lidocaine gel in Ghana since the main raw material can be locally sourced. A non-inferiority testing is best suited for this comparative study since the 2% Lidocaine gel is a standardized lubricant which has been used frequently in trials. Despite limitations, we believe the SHEA-LIDO trial is well designed and will yield important results

1 Introduction

Medical lubricants are essential tools to the physician. In choosing a lubricant for a medical procedure, it should be appropriate for the purpose. It should be physiologically inert and stable at room and extreme pressures [1]. A number of substances have been used as lubricants including glycerol, emulsions, propylene glycol, oils and gels.

Lidocaine and K-Y gels are the predominant lubricants use for surgical procedures in Ghanaian hospitals. However, the cost and procurement delays have led to the chronic unavailability of these materials. Physicians therefore resort to the usage of inappropriate products to get around the situation. The use of inappropriate materials such as soapy water, chlorhexidine solutions, plain water and methylated spirit have led to considerable discomfort and pain to patients. Shea butter, which is locally produced, cheaper and readily available, when adequately processed and sterilized, may serve as a good substitute to the aforementioned products due to its similar constituents. To the best of our knowledge, data on the use of shea butter as a medical lubricant is lacking. Our vision is to transform this raw material into a refined product which can be used for procedures in Ghanaian hospitals and other medical facilities worldwide provided it met the required safety and biomedical standards.

A cost analysis also showed that 2% lidocaine gel is more expensive than plain lubricants. Chen and coworkers [2] reported that the cost of 2% lidocaine gel is about three times that of plain gel even though lidocaine gel had no edge over the ordinary lubricant. The cost per 100ml of 2% lidocaine gel and plain lubricant was 220 and 66.6 Taiwan dollars respectively (in 2005). Mcfarlene and colleagues [3] also confirmed the relatively high cost of 2% lidocaine gel at their institution. It emerged that cost savings could be more than GBP 3,876 (USD 5,000) per year if 2% lidocaine gel was eliminated from cystoscopy examinations. A 30g tube of 2% lidocaine gel on the Ghanaian market cost an average of USD 5.00.

This novel shea lubricant is constituted from refined shea olein. Added to this is an acrylic acid polymer, an emulsifier (propylene glycol) and preservatives (methyl paraben and propyl paraben) to achieve a unique blend. It is sterilized by heating and stored under room temperature conditions away from direct sunshine. The product has also been subjected to physiochemical and microbiological analysis and stored in a collapsible sealed plastic tube.

In this randomized single blind non-inferiority trial we seek to compare the effectiveness, lubricity and complications of a novel shea lubricant to 2% Lidocaine gel during digital rectal examination.

2 Methods/design

2.1 Study design

The Shea-Lido trial is a randomized single blind, non-inferiority trial which seeks to compare the effectiveness in pain reduction, the lubricity and complications of a novel shea lubricant to 2% lidocaine gel during digital rectal examination. The trial was approved by the University of Health and Allied Sciences, Research Ethics Committee with protocol number UHAS-REC A. 2(4) 20 – 2 [4] and will be conducted in accordance with the Declaration of Helsinki. It has been registered with the Pan African Clinical Trials Registry with the unique identification number PACTR202011687956222 [5] and the Food and Drugs Authority (FDA) Ghana Clinical Trials Registry with certificate number FDA/CT/217. The investigational product (shea lubricant) underwent physiochemical and microbiological analysis at the

Ghana Standards Authority. The certificate of analysis (COA) of the control lubricant was similarly verified by FDA, Ghana.

The SHEA-LIDO trial will enroll a minimum of 152 patients at the Ho Teaching Hospital. This teaching hospital attends to an average of 170,000 patients annually. Participants will be randomized to two treatment arms, the shea lubricant and the 2% Lidocaine gel arms. These patients will be followed up for a minimum period of 1 year after enrollment to observe for adverse effect or complications resulting from treatment.

2.2 Study oversight

Two bodies will oversee the SHEA-LIDO trial. The steering committee comprising four physicians/investigators of the study, will be responsible for supervising the trial. This includes site selection, training of trial nurses and doctors, the quality of trial, preservation of investigational lubricants, randomization of participants, enrollment and maintenance of the study protocol.

The Data and Safety Monitoring Board (DSMB), comprising four members, two surgeons, a DSMB biostatistician and an independent biostatistician. The DSMB is restricted to individuals free of any conflict of interest. The DSMB has stewardship over review of participant recruitment, accrual, retention and withdrawal. It also has responsibility for monitoring the safety and well-being of the study participants, ensuring the scientific integrity and adherence to study protocols.

2.3 Study population

Male and female patients between 18 and 80 years of age, presenting to the urology, emergency and surgical units of the Ho Teaching Hospital for whom a digital rectal examination is indicated, could understand the survey process and consents to the study will be screened. Individuals with painful anal conditions such as thrombosed haemorrhoids, anal fissures, anal cancers and strictures as well as those too ill to communicate/consent will be excluded. Adverse events will be collated throughout the entire period of the study. The DSMB, the FDA-Ghana will be appropriately informed of any adverse events that may occur from the use of the lubricant.

2.4 Objectives

This study aims to compare the level of lubricity, complications and pain reduction effect of a novel shea lubricant to 2% Lidocaine gel for digital rectal examination.

2.5 Hypothesis

Our hypothesis is to test whether the shea lubricant can achieve the same level of pain reduction as obtained with the use of 2% lidocaine gel for digital rectal examination, at a better ease of performing the procedure. The confirmation of non-inferiority involved the pre-specification of a mean pain difference for shea lubricant as compared to 2% lidocaine gel below a predefined margin, based on a relative measure. The non-inferiority (NI) margin was defined such that the mean pain difference between the two lubricants was no worse that − 0.72 on the visual analogue scale. This limit was determined using 50%

discount of the lower limit of the 95% confidence interval of the mean pain reduction effect of the control lubricant from a previous study [6] as recommended by the 95% − 95% fixed margin approach [7]

Δ NI = -0.72

Null hypothesis: $\Delta \geq \Delta$ NI

Alternate hypothesis: $\Delta < \Delta$ NI

Primary outcome measure is to determine the mean difference in pain perception during the procedure with a non-inferiority limit set at -0.72.

Secondary outcome measures include assessing the differences in the perception of discomfort, peri-anal pruritus, bowel and urinary urgency during the procedure using Likert scales. Secondly, to assess the ease of use of the lubricants by trial doctors.

2.6 Determination of sample size

In the estimation of the sample size, we considered the standard deviations for pain perception after catheterization from a previous study done by Stav et al [8], a randomized controlled trial comparing pain perception of 2% lidocaine gel to liquid Paraffin oil. We chose this study because it compared an oil-based lubricant to lidocaine gel, which is the intent of the present study. To determine the non-inferiority limit, we relied on a systematic review and meta-analysis by Hong et al [13] where the mean difference for pain was estimated at -0.96 (95% confidence interval, -1.43 to -0.49) after including sixteen randomized trials. Thus non-inferiority limit was set at -0.72 which is a 50% discount of the lower limit of the 95% confidence interval (-1.43) of the mean pain reduction effect of the control lubricant (2% lidocaine gel); as shown in literature [7]. An attempt to ensure that the shea lubricant preserved at least half the effect of 2% lidocaine gel. The trial was therefore designed to randomly allocate 152 patients with 90% certainty (power), assuming that the lower limit of the 95% confidence interval was within a prespecified boundary of -0.72 in mean pain perception difference using the visual analogue scale, with a 1:1 allocation ratio and $\mu_1 - \mu_2$= 0 for non-inferiority trials, as shown in literature [9][10].

2.7 Trial process

Trial doctors and nurses will be recruited. To ensure quality control, reliability and reproducibility, the trial recruits will be trained in data collection, trial protocols and procedures, seeking informed consent and safe disposal of waste. The investigational products are to be stored at the hospital's pharmacy under ambient conditions. The lubricants will be prepared by the independent trial nurses, and delivered in marked 5ml –syringes, labelled A and B to trial doctors.

All DRE examinations are to be done in the presence of a chaperone due to the sensitivity of the procedure. After explaining the procedure and seeking consent, participants will be requested to undress including undergarments in privacy and a gown used to preserve modesty. Patients will lie on a couch in the left lateral position facing away from the examiner with the legs drawn up towards the chest. The

examiner puts on sterile gloves and the examination starts with inspection of the natal clefts (the groove between the buttocks), the anus and the perianal skin for lesions. Any lesion that constitute a contraindication (refer to inclusion/exclusion criteria) leads to an abandonment of the procedure. The patient will be asked to bear down; observing for lesions. The examiner lubricates the examining finger with 5 mls of the selected lubricant. At this stage, the examiner alerts the patient about the commencement of the procedure. The examiner will gently pat the buttocks and applies gentle pressure at the anal margin to enter the anus and the rectum. The anal tone is determined by asking the patients to "squeeze" on the examining finger and release. The finger is then directed posteriorly following the curve of the sacrum observing for any lesions, tenderness, tightness and mobility of the rectal mucosa. The finger will then be swept anteriorly in a clockwise direction to examine the prostate in men and pouch of douglas in women. The examination is completed by inspecting the examining finger for the nature of faecal matter, streaks of blood or any discharge.

2.8 Sampling procedure

Male and female patients, between ages 18 and 80 who will present to the Emergency, Urological and Surgical units for whom a digital rectal examination is indicated, meets our eligibility criteria and consents to participate will be invited. There will be two treatment arms, Shea Lubricant (A) and 2% lidocaine gel (B). A clinical trial randomization software (National Cancer Institute Clinical Trial Randomization tool) will be employed to allocate patients to the two groups using a 1:1 allocation ratio. Patients assigned odd numbers will be randomized to Group A and those assigned an even number, to Group B. The process will continue till the required number of participants are obtained in the two groups. The examination procedure is explained after informed consent [11] has been sought. Participants will be assured of their privacy, confidentiality and their rights to opt out of the trial at any point time without affecting their access to quality care. Structured questionnaires [12] are then administered before, immediately and 30 minutes after the procedure to assess pain perception, peri-anal discomfort and pruritus, urinary and bowel urgency. The questionnaire will also evaluate trial doctors' assessment of 'ease of use' of the lubricants.

2.9 Stopping rules

Our stopping criteria are based on three ethical principles- safety, benefit or futility of the trial. Development of serious adverse events such as anaphylactic shock, urticaria, wheezing attacks or any other form of serious adverse drug reaction will trigger a discontinuation. Furthermore, any indication of futility or supremacy of the shea lubricant will trigger trial discontinuation.

2.10 Insurance cover

In order to ensure patient safety and protection, participants will be insured against any liabilities and duly compensated for any physical damage that may emanate from their participation. This will cover the period of trial.

2.11 Methods of randomization and data collection

A minimum of 152 participants are expected. A clinical trial randomization tool will allocate patients to the two groups in a 1:1 allocation ratio. The allocation sequence will be concealed from trial doctors and nurses, and only revealed to the trial nurse upon the recruitment of a participant while keeping the trial doctor in oblivion. The sequence will be generated by an investigator assigned for that purpose whilst the trial nurses will enroll, assigned participants to an intervention and also assess outcome. Study participants will be blinded to the interventions however trial doctors may not be blinded since the investigational products are different in consistency. The study will use a quantitative data collection approach. A structured questionnaire consisting of three sections 1) socio-demographic characteristics 2) patients' perception 3) ease of use of the lubricants will be employed. Patients' perception of anal pain will be evaluated with a Visual analogue scale which rates pain from the most excruciating (10) to no pain (0). Peri-anal discomfort, pruritus, bowel and urinary urgency are assessed using Likert scales to each of the questions. Similarly, a Likert scale will determine the ease of use of lubricants by clinicians. Questionnaires will be administered through face-to-face interviews after written informed consent is obtained with the privacy, confidentiality and security of patients' data assured. Data collated will be entered into Excel 2013 and exported to SPSS 25 and R 4.1.2 for analysis. Quality control measures to be instituted prior to data collection include 1. Training of research assistants, trial doctors and nurses on data collection and informed consent 2. Error correction 3. Appropriate storage of investigational products. The data collected will be entered daily and validated.

2.12 Data analysis

The table below summarizes the study variables and the estimation approach

Table 1
Summary of analyses of patients' perception

Perception	Tool	Estimation approach
Anal pain	Visual analogue scale (V.A.S)	A V.A.S tool assesses the perception of pain felt by patients during digital rectal examination. The scale rates pain from 0 (no pain) to 10 (worst imaginable pain). The mean score will be determined by summing up the score in each group and dividing by the number of participants in that group. The mean difference in pain score is then deduced and compared to the non-inferiority limit of -0.72 to ascertain inferiority or otherwise of the shea lubricant.
Peri-anal discomfort and pruritus	Likert scale	To estimate these variables, a 4-dimension Likert scale will be adopted (i.e., [1] Nil, [2] Mild, [3] Moderate [4] Severe) in relation to the level of peri-anal discomfort and pruritus perceived by patients in the two arms. Mean scores in both groups are then compared to determine difference in perception.
Urinary and bowel urgency	Likert scale	The urinary and bowel urgency score are obtained from responses to 4-dimension Likert scales (i.e., [1] Nil, [2] Mild, [3] Moderate [4] Severe) in relation to the perceptions of urinary and bowel urgency experienced by participants.
Ease of use of Lubricants and Lubricity	Likert scale	Trial doctors will assess the ease of use of lubricants and lubricity using a 5-dimension Likert scale (i.e. [1] Effortless, [2] Easy, [3] Fair, [4] Difficult and [5] Very difficult). The scores achieved for each option are expressed as mean scores. The proportions obtained for dimensions in each group are then compared.

2.13 Statistical analysis

The collated data will be exported to SPSS 25 and R 4.1.2 for analysis. Friedman test assesses the mean ranks before, during and after the procedure, whilst Wilcoxon signed-rank test will compare two dependent groups. Mann Whitney test will compare two independent groups. Categorical variables will be reported using frequency tables and charts while continuous variables will be reported using means and standard deviations. The primary end point is the mean difference in pain intensity experienced in the two groups, ascertained using the Visual analogue scale whilst the secondary end points, that is, differences in discomfort, peri-anal pruritus, bowel and urinary urgency will be determined using a 4 point-rated Likert scale. The study end points will be analyzed for the per-protocol population. A sensitivity analysis will then be conducted for the intention-to-treat population. For the primary end point analysis, a 95% confidence interval with a two-sided 5% level of significance approach will be employed. To establish non-inferiority of shea lubricant to 2% lidocaine gel, the lower limit of the 95% confidence interval should be above the non-inferiority limit set at -0.72. The non-inferiority test will be performed for only the primary end point and the secondary end points analyzed for superiority.

3 Discussion

Lidocaine and K-Y gels are commonly used in Ghanaian hospitals albeit at high cost to patients and the health system. The cost of 2% Lidocaine gel has been estimated to be at least three times that of plain gel in some jurisdictions [2]. Even more, significant cost savings could be made if Lidocaine gels are eliminated from cystoscopy examinations [3]. The cost of a 10ml tube of 2% Lidocaine gel on the Ghanaian market is estimated to USD 5.00 while the cost of production of a 100ml tube of the Shea lubricant is USD 0.71. The Shea lubricant can be substituted for 2% Lidocaine gel in Ghana, provided it met required standards since the main raw material can be locally sourced.

A non-inferiority testing is best suited for this comparative study since the 2% Lidocaine gel is a standardized lubricant which has been used frequently in trials [6][8]. The Shea lubricant, a novel product may serve as a substitute if it could preserve at least half the pain reduction effect of the 2% Lidocaine gel. The advantages of the shea lubricant mainly readily available and low cost of production obligates us to investigate further. Our trial is adequately powered (90% certainty) to discriminate between inferiority and non-inferiority of the investigational products with a non-inferiority margin which was determined through stringent statistical evaluation of the available literature.

Our trial will generate evidence that may support the use of a shea butter as a medical lubricant since this is lacking in literature. This may inform efforts at finding home-based substitutions to imported products. It may also serve as a launch pad for further research in this uncharted area of medicine.

The study has some limitations. The difference in the consistency of investigational products meant that trial doctors cannot be blinded to the study lubricants which may impact outcome. The primary and secondary end points include important objectives that may warrant further testing in larger cohorts. In future, it may be necessary to test the efficacy of the shea lubricants in other procedures such as nasogastric tube passage and urethral catheterization.

Despite the aforementioned limitations, we believe the SHEA-LIDO trial is well designed and will yield important results.

Declarations

Competing interest

The authors declare no competing interest

References

1. Bartnett C.A;The optimal selection and use of surgical instrument lubricants (May):34–7 (2008)

2. Chen YT.et al. Randomized double-blind comparison of lidocaine gel and plain lubricating gel in relieving pain during flexible cystoscopy. J Urol. 175(4):1375 (2006).

3. Liebert MA, Farlane NMC, Denstedt J, Ganapathy S, Razvi H. Lidocaine Gel and Placebo in Men Undergoing Flexible Cystoscopy. 15(5) (2001).

4. Appendix I : Ethical clearance certificate for the SHEA LIDO trial

5 Appendix II : Trial registration cerficate

6. Hong H, Kim G, Lee H, Lee A. Pain Reduction Effects of Lidocaine Gel for Urethral Catheterization : A Systematic Review and Meta-Analysis. 18(6):438–48 (2017).

7. Services H.;. FDA Guidance non-inferiority clinical trials. November (2016)

8. Siderias J, Guadio F, Singer AJ. Comparison of topical anesthetics and lubricants prior to urethral catheterization in males: A randomized controlled trial. Acad Emerg Med. 11(6):703–6(2004).

9. Lesaffre E. Superiority, Equivalence and Non-inferiority Trials : Bulletin of the NYU Hospital for Joint Diseases 2008;66(2):150-4 (2008)

10. Pinto VF. Non-inferiority clinical trials: Concepts and issues. J Vasc Bras. 9(3):145–51(2010).

11. Appendix III: Informed consent form for the SHEA LIDO trial

12. Appendix IV: Questionnaire form for the SHEA LIDO trial.

Figures

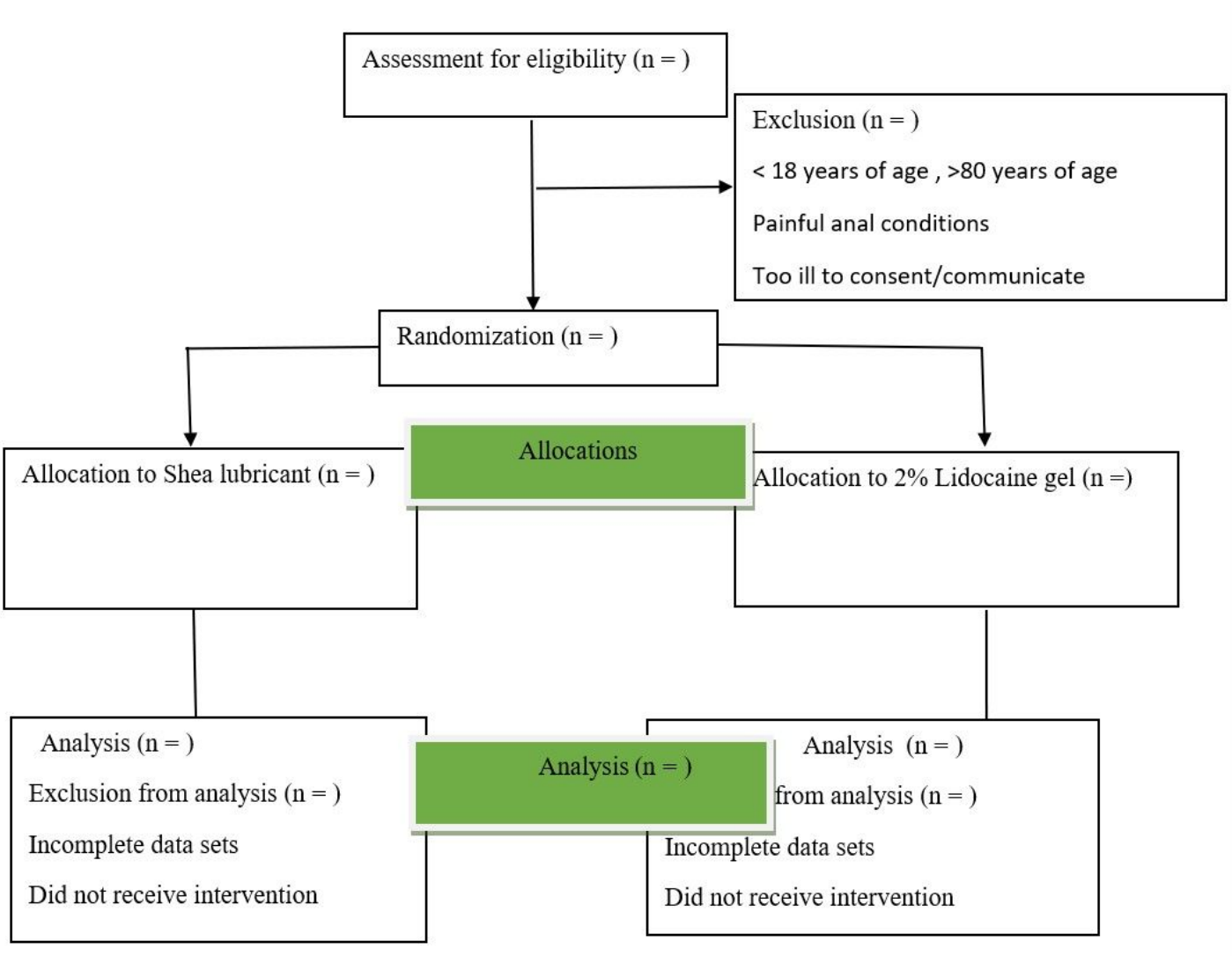

Figure 1

Study design overview

Supplementary Files

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

- Appendixlethicspreprint.docx
- AppendixIlregistrationpreprint.docx
- Questionnaire.doc
- Informedconsent.doc