Effect of EUSOL dressings on Healing Rate in Wounds Healing by Secondary Intention

Naveed Pasha [naveedpash@gmail.com](mailto:naveedpash@gmail.com)

March 1, 2019

Abstract here ---

# Introduction

Smith et al. describe the Edinburgh University Solution of Lime (EUSOL) to be a highly diluted weak acid comprising 1.99 percent EUSOL against 98.01 percent water. The exact constituents of the Edinburgh University Solution of Lime are 0.54 percent hypochlorous acid, 1.28 percent calcium biborate and 0.17 percent calcium chloride. Therefore, it is essentially formed of the chemical reaction of boric and chlorate salts. In this chemical composition, EUSOL is volatile and decomposes into hypochlorous acid and sodium chloride. This process is accelerated in the presence of light therefore EUSOL is stored in photo-resistant containers. ([1](#bibliography-default-Smith_1915))

## Mode of Action

The antiseptic properties of EUSOL were known as far back as 1990s whereby experiments show its effectiveness against streptococcus pyogenes among other pathogens. EUSOL has even been investigated as an intravenous agent in the treatment of the bubonic plague. ([2](#bibliography-default-connor1916eusol))

Recently, EUSOL has also come to be known as a chemical debridement agent. ([3](#bibliography-default-Farrow_1991)) It loosens slough (fibrinous, necrotic cellular debris) from the base of the wound. In doing so, it prevents the retardation of wound granulation (ingrowth of new fibroblasts) and epithelialisation (regeneration of the outermost layer of the skin). This theoretically reduces the time to wound healing. It also decreases the chance of wound infection as decreased slough means reduced nidus of bacterial colonisation.

# Rationale

Wounds healing by secondary intention are at risk of developing a layer of fibrinous exudate (commonly termed as "slough"). Slough has the potential to arrest the formation of healthy granulation tissue as well as to elevate the risk of wound super-infection. Meticulous wound dressing involves addressing the appearance of slough on wound in order to mitigate the risks of delayed wound healing and wound super-infection. The Edinburgh University Solution of Lime is commonly added to dressing routines as a method of chemical debridement of slough.

Several problems remain with the use of EUSOL. The foremost problem is that EUSOL is expensive with the cost of averaging to 3 rupees per milliliter. This price may not be problematic for small wounds that require once daily dressing. However the price can climb steeply if the wounds are of large size or require multiple dressings within 24 hours.

Another problem, as detailed above, is that the chemical composition of EUSOL degrades with time. Therefore EUSOL cannot be purchased or stored in bulk quantity. Not all patients have the capacity to visit a pharmacy repeatedly to obtained more EUSOL when expired and this is especially a problem for patients living in remote areas.

Perhaps the most concerning point on using EUSOL for wound care is that its efficacy has remained controversial for well more than a decade. One of the first objections to the use of EUSOL for wound dressings appears in the 1990s. ([4](#bibliography-default-Burton_1992),[5](#bibliography-default-Patton_1992)) These objections are narrated in letters to the editors where doctors describe events where they have been approached by other healthcare providers either discouraging or actively refusing the use of EUSOL in patient care. The NICE guidelines (NICE, 2019) categorically prohibits the use of EUSOL on wounds that are healing by secondary intention.

However, it is difficult to synthesize an evidence based opinion regarding EUSOL from the literature. To the knowledge of the authors, there exists no study directly comparing EUSOL dressing with simple gauze soaked in normal saline. Rather, all available studies focus on comparison of EUSOL dressing with a variety of other dressing materials. Table 1 summarises these studies.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study Author & Year | Control Group | Reported Outcome | Outcome of Cases | Outcome in Controls | Number of Cases | Number of Controls |
| Bajaj et al., 2009 ([6](#bibliography-default-Bajaj_2009)) | Sugar Coated Dressing | Wound size at week 4 (mm) | 77 ± 97.28 | 104 ± 130.54 | 24 | 26 |
| Goode et al., 1979 ([7](#bibliography-default-Smith_2013)) | Dextranomer Beads | Time to clean wound bed (days) | 11.6 | 8.1 | 10 | 10 |
| Groenwald et al., 1980 ([8](#bibliography-default-Gethin_2015)) |  |  | 15.4 | 5.9 | 50 | 50 |
| Soderberg et al., 1982 ([9](#bibliography-default-Reinar_2019)) | Zinc Tape | Healing of ulcers (days) | 30 (21 - 63) | 17 (12 - 20) | 42 | 48 |

Table: Summary of literature comparing EUSOL with various other wound dressing materials.

It is immediately obvious that no unified conclusion can be drawn from these studies. There is no single, uniform measure of wound healing across studies to allow objective comparison of the relative performance of EUSOL. Furthermore, none of the dressings materials described in these studies are commonly used in Pakistan for dressing wounds healing by secondary intention.

In summary, the rationale of this study is the need for effective and inexpensive dressing to address the slough that frequently appears on surgical wounds healing by secondary intention.

## Study Hypotheses

The null hypothesis is that the healing rate of open surgical wounds dressed with EUSOL dressings is not greater than that of open surgical wounds dressed with Normal Saline dressings.

The alternate hypothesis is that the healing rate of open surgical wounds dressed with EUSOL dressings is greater than that of open surgical wounds dressed with Normal Saline dressings

# Methods and Materials

## Operational Definitions

* **Wound Healing Rate**: A wound care practitioner will measure the two longest diameters for every wound, *a* and *b*, such that *a* and *b* are mutually perpendicular. The diameters will be measured in millimeters. The diameters will be measured once every week for a total of six weeks from the time of the patients' surgery. The wound healing rate will then be calculated as the advance of the wound margin towards the center of the wound, in mm per day, using the formula where is the area of the wound on the zeroth day given by and is the perimeter of the wound on the zeroth day given by ] and is the predicted time of wound closure ([11](#bibliography-default-Cukjati_2001))
* **Predicted Time of Wound Closure**: The predicted time, in days, for a given wound to reduce to 5% of its initial area or the predicted time for a given wound to reduce to less than 100 mm2 which ever is smaller. This definition has been adapted from Cukjati et al. and will be calculated according to their method. ([11](#bibliography-default-Cukjati_2001))
* **Diabetic Patient**: Patients with reduced ability to auto-regulate serum glucose levels as defined by guidelines of the National Institute of Health and Care Excellence, United Kingdom ([12](#bibliography-default-ICGT_2015)):
  + Documented fasting blood glucose level > 125 mg/dL
  + Documented random blood glucose level > 200 mg/dL
  + Documented HbA1c > 6.5 mg/dL
  + Taking oral hypoglycemic agents
  + Taking subcutaneous insulin injection
* **Smoking Status and Cigarette Usage**: Cigarette usage as defined by the Centers of Disease Control and Prevention, USA ([13](#bibliography-default-CDC_Smoking))
  + Every day smoker: An adult who has smoked at least 100 cigarettes in his or her lifetime, and who now smokes every day. Previously called a “regular smoker”.
  + Former smoker: An adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview.
  + Never smoker: An adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime.
* **Normal Saline Dressing**: The practice of applying povidone-iodine to wound edges followed by washing wounds with at least 500 cc of normal saline before applying gauze in a clean or sterile fashion
* **EUSOL Dressing**: The practice of applying povidone-iodine to wound edges followed by washing wounds with at least 500 cc of normal saline before applying gauze soaked in EUSOL in a clean or sterile fashion
* **Open Surgical Wound**: Surgical wound where skin has not been approximated by staples or sutures
* **Wound Care Practitioner**: Wound Nurses, surgeons and/or surgical residents with at least one year of experience in dressing surgical wounds healing by secondary intention

## Primary Objective

To determine whether the healing rate of open surgical wounds healing by secondary intention is significantly greater with EUSOL dressing as compared to normal saline dressing.

## Outcome Measure

The main outcome measure of this study will be mean healing rate. Healing rate will be calculated as defined by Cukjati et al. The authors have briefly paraphrase this method of calculation in the "Operational Definitions" section for the benefit of the reader who is referred to the full text for complete details. The mean healing rate of the patients treated with normal saline dressings and patients treated with EUSOL dressings will be compared for any significant difference.

## Study Design

This will be a single center, double-blinded, non-placebo-controlled, parallel-group study with balanced randomisation (1:1). The study will be conducted in Karachi, Pakistan whereby patients will be followed during both in-hospital stay as well as outpatients for a total of six weeks after surgery.

The unblinded data collected from each group will be reviewed by an independent Data Monitoring Committee for patient safety. This independent Data Monitoring Committee will be responsible for interim analysis of the data that may This study will follow surgical wounds left to heal by secondary intention. Therefore the study setting will be the Aga Khan University Hospital for inpatients as well as patients receiving home healthcare in the city of Karachi.

## Inclusion Criteria

This study will include adult, post-operative patients with surgical wounds of the abdomen and limbs that have been left to heal by secondary intention.

## Exclusion Criteria

Patients with the following types of wounds will be excluded from this study:

* Wounds resulting from and/or complicated by viscero-cutaneous fistula: These wounds involve an abnormal connection between the epithelium of the skin and the epithelium of a hollow viscus that normally produces a bodily fluid. Wound care of viscero-cutaneous fistulas involves maneuvers to abate the physical and chemical effects of the bodily fluid to the skin. Such maneuvers have little or no connection with EUSOL. Therefore, wounds related to viscero-cutaneous fistulas are beyond the scope of this study.
* Wounds resulting from pre-existing dermatological pathology, for example (but not limited to) psoriasis: Wounds resulting from pre-existing dermatological pathology have a different natural history of healing as compared to wounds on otherwise normal skin. Management of such wounds typically involves medical regimens tailored to curtail the pathology causing the wound and wound healing is directly correlated to controlling that pathology. Therefore, these wounds are beyond the scope of this study.

## Sampling Technique

This study will recruit patients using consecutive sampling. Informed consent will be taken from patients who have undergone surgery whereby the surgical wound was left open. Recruitment will be attempted immediately in the immediate post-operative period which spans 24 - 48 hours after surgery.

## Randomisation Technique

The patients will be randomly assigned to one of following two parallel groups in a 1:1 ratio:

* Normal Saline Dressings
* EUSOL Dressings

Randomisation will be stratified by diabetic status, smoking status and presence of peripheral arterial disease. Following stratification, randomisation will be done using block randomisation technique using blocks of four, six and eight patients as follows:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Block Identifier | Block Size | Sequence Within Block | Treatment | Diabetes | Smoker | PAD | Randomisation Code |
| 1 | 8 | 1 | EUSOL | Yes | Yes | Yes | MH1 |
| 1 | 8 | 2 | EUSOL | Yes | Yes | Yes | AQ4 |
| 1 | 8 | 3 | Normal Saline | Yes | Yes | Yes | GO6 |
| 1 | 8 | 4 | Normal Saline | Yes | Yes | Yes | ZV5 |
| 1 | 8 | 5 | Normal Saline | Yes | Yes | Yes | MA2 |
| 1 | 8 | 6 | EUSOL | Yes | Yes | Yes | EO8 |
| 1 | 8 | 7 | Normal Saline | Yes | Yes | Yes | MZ6 |
| 1 | 8 | 8 | EUSOL | Yes | Yes | Yes | FQ0 |
| 2 | 6 | 1 | EUSOL | Yes | Yes | No | BL7 |
| 2 | 6 | 2 | Normal Saline | Yes | Yes | No | VF3 |
| 2 | 6 | 3 | Normal Saline | Yes | Yes | No | JL2 |
| 2 | 6 | 4 | EUSOL | Yes | Yes | No | LY2 |
| 2 | 6 | 5 | Normal Saline | Yes | Yes | No | YX4 |
| 2 | 6 | 6 | EUSOL | Yes | Yes | No | OZ5 |
| 3 | 8 | 1 | Normal Saline | Yes | Yes | No | ZU6 |
| 3 | 8 | 2 | EUSOL | Yes | Yes | No | PM5 |
| 3 | 8 | 3 | Normal Saline | Yes | Yes | No | ZN4 |
| 3 | 8 | 4 | Normal Saline | Yes | Yes | No | YE2 |
| 3 | 8 | 5 | Normal Saline | Yes | Yes | No | ND6 |
| 3 | 8 | 6 | EUSOL | Yes | Yes | No | BS6 |
| 3 | 8 | 7 | EUSOL | Yes | Yes | No | JY9 |
| 3 | 8 | 8 | EUSOL | Yes | Yes | No | LI5 |
| 4 | 4 | 1 | Normal Saline | Yes | No | Yes | TT4 |
| 4 | 4 | 2 | EUSOL | Yes | No | Yes | LC5 |
| 4 | 4 | 3 | Normal Saline | Yes | No | Yes | EO2 |
| 4 | 4 | 4 | EUSOL | Yes | No | Yes | NU7 |
| 5 | 8 | 1 | Normal Saline | Yes | No | Yes | ZW1 |
| 5 | 8 | 2 | EUSOL | Yes | No | Yes | XL9 |
| 5 | 8 | 3 | Normal Saline | Yes | No | Yes | MQ3 |
| 5 | 8 | 4 | Normal Saline | Yes | No | Yes | KL2 |
| 5 | 8 | 5 | Normal Saline | Yes | No | Yes | OJ7 |
| 5 | 8 | 6 | EUSOL | Yes | No | Yes | HR8 |
| 5 | 8 | 7 | EUSOL | Yes | No | Yes | OL4 |
| 5 | 8 | 8 | EUSOL | Yes | No | Yes | DE6 |
| 6 | 8 | 1 | EUSOL | Yes | No | No | LS1 |
| 6 | 8 | 2 | Normal Saline | Yes | No | No | SE1 |
| 6 | 8 | 3 | Normal Saline | Yes | No | No | YZ1 |
| 6 | 8 | 4 | EUSOL | Yes | No | No | EQ3 |
| 6 | 8 | 5 | Normal Saline | Yes | No | No | SS0 |
| 6 | 8 | 6 | EUSOL | Yes | No | No | NA6 |
| 6 | 8 | 7 | EUSOL | Yes | No | No | RO2 |
| 6 | 8 | 8 | Normal Saline | Yes | No | No | YT0 |
| 7 | 4 | 1 | EUSOL | No | Yes | Yes | SV3 |
| 7 | 4 | 2 | EUSOL | No | Yes | Yes | LU0 |
| 7 | 4 | 3 | Normal Saline | No | Yes | Yes | YB5 |
| 7 | 4 | 4 | Normal Saline | No | Yes | Yes | OC4 |
| 8 | 4 | 1 | Normal Saline | No | Yes | Yes | FL2 |
| 8 | 4 | 2 | EUSOL | No | Yes | Yes | CH4 |
| 8 | 4 | 3 | Normal Saline | No | Yes | Yes | RX4 |
| 8 | 4 | 4 | EUSOL | No | Yes | Yes | QQ6 |
| 9 | 8 | 1 | EUSOL | No | Yes | No | AE6 |
| 9 | 8 | 2 | Normal Saline | No | Yes | No | PR0 |
| 9 | 8 | 3 | Normal Saline | No | Yes | No | TO6 |
| 9 | 8 | 4 | Normal Saline | No | Yes | No | WT8 |
| 9 | 8 | 5 | Normal Saline | No | Yes | No | ZI8 |
| 9 | 8 | 6 | EUSOL | No | Yes | No | CZ5 |
| 9 | 8 | 7 | EUSOL | No | Yes | No | XQ8 |
| 9 | 8 | 8 | EUSOL | No | Yes | No | RA6 |
| 10 | 4 | 1 | EUSOL | No | No | Yes | GN6 |
| 10 | 4 | 2 | Normal Saline | No | No | Yes | NN4 |
| 10 | 4 | 3 | Normal Saline | No | No | Yes | LZ8 |
| 10 | 4 | 4 | EUSOL | No | No | Yes | WT7 |
| 11 | 8 | 1 | Normal Saline | No | No | Yes | NL7 |
| 11 | 8 | 2 | Normal Saline | No | No | Yes | HG6 |
| 11 | 8 | 3 | EUSOL | No | No | Yes | KZ2 |
| 11 | 8 | 4 | Normal Saline | No | No | Yes | MZ4 |
| 11 | 8 | 5 | EUSOL | No | No | Yes | RW1 |
| 11 | 8 | 6 | Normal Saline | No | No | Yes | CH7 |
| 11 | 8 | 7 | EUSOL | No | No | Yes | FY3 |
| 11 | 8 | 8 | EUSOL | No | No | Yes | WE1 |
| 12 | 4 | 1 | Normal Saline | No | No | No | RU1 |
| 12 | 4 | 2 | Normal Saline | No | No | No | JQ6 |
| 12 | 4 | 3 | EUSOL | No | No | No | GL7 |
| 12 | 4 | 4 | EUSOL | No | No | No | UF9 |
| 13 | 6 | 1 | EUSOL | No | No | No | NN5 |
| 13 | 6 | 2 | EUSOL | No | No | No | FB9 |
| 13 | 6 | 3 | EUSOL | No | No | No | AO2 |
| 13 | 6 | 4 | Normal Saline | No | No | No | EE2 |
| 13 | 6 | 5 | Normal Saline | No | No | No | EF4 |
| 13 | 6 | 6 | Normal Saline | No | No | No | QK3 |

Patients will be selected upon presentation to the Aga Khan University Hospital using block permutation method. Two blocks of 4 subjects each will be used. Upon selection, patients will be randomised to one of the following two study groups:

Randomisation will be stratified according to diabetic status. Cases will be matched with controls on the basis of diabetic status, smoking status and wound size.

## Sample Size

The sample size for this study had been calculated on the basis of the work of Bajaj et al. ([6](#bibliography-default-Bajaj_2009)) who compared the rate of wound healing in patients treated with sugar coated bandages with that of patients treated with EUSOL dressing. To the authors' best knowledge, there is no other study that more closely resembles the objectives of this study. Therefore, the authors saw fit to base sample size calculation upon this study.

Based on this study, the anticipated proportion of patients with wound healing in the standard dressing group (case group) is 77% and the anticipated proportion of patients with wound healing in the EUSOL dressing group (control group). Thus the relative risk of wound healing from normal saline dressing versus EUSOL dressing is expected to be 1.2.

The sample size was calculated using OpenEpi Software version 3.01. The sample size was calculated using the above anticipated proportions as well as significance of 5%, power of 80% and an inflation of 10% to account for non-response. The minimum sample size required was calculated to be 532 patients in total: 266 patients in Group 1 (standard dressing) and 266 patients in Group 2 (EUSOL dressing).

image::sample-size.png[Snapshot of Sample Size calculated with OpenEpi]

# References

1. Smith JL, Drennan AM, Rettie T, Campbell W. Experimental Observations ON THE ANTISEPTIC ACTION OF HYPOCHLOROUS ACID AND ITS APPLICATION TO WOUND TREATMENT. BMJ [Internet]. 1915Jul;2(2847):129–36. Available from: <https://doi.org/10.1136%2Fbmj.2.2847.129>

2. Connor FP. Eusol and Plague: A Suggestion. The Indian Medical Gazette. 1916;51(2):73.

3. Farrow S, Toth B. The place of Eusol in wound management. Nursing Standard [Internet]. 1991Feb;5(22):25–6. Available from: <https://doi.org/10.7748%2Fns.5.22.25.s39>

4. Burton JL. For and against Eusol. BMJ [Internet]. 1992May;304(6839):1442–3. Available from: <https://doi.org/10.1136%2Fbmj.304.6839.1442-b>

5. Patton MA. Eusol: the continuing controversy. BMJ [Internet]. 1992Jun;304(6842):1636–. Available from: <https://doi.org/10.1136%2Fbmj.304.6842.1636-a>

6. Bajaj G, Karn NK, Shrestha BP, Kumar P, Singh MP. A randomised controlled trial comparing eusol and sugar as dressing agents in the treatment of traumatic wounds. Tropical Doctor [Internet]. 2009Jan;39(1):1–3. Available from: <https://doi.org/10.1258%2Ftd.2008.080322>

7. Smith F, Dryburgh N, Donaldson J, Mitchell M. Debridement for surgical wounds. Cochrane Database of Systematic Reviews [Internet]. 2013Sep; Available from: <https://doi.org/10.1002%2F14651858.cd006214.pub4>

8. Gethin G, Cowman S, Kolbach DN. Debridement for venous leg ulcers. Cochrane Database of Systematic Reviews [Internet]. 2015Sep; Available from: <https://doi.org/10.1002%2F14651858.cd008599.pub2>

9. Reinar LM, Forsetlund L, Lehman LF, Brurberg KG. Interventions for ulceration and other skin changes caused by nerve damage in leprosy. Cochrane Database of Systematic Reviews [Internet]. 2019Jul; Available from: <https://doi.org/10.1002%2F14651858.cd012235.pub2>

10. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. Cochrane Database of Systematic Reviews [Internet]. 2015Mar; Available from: <https://doi.org/10.1002%2F14651858.cd005083.pub4>

11. Cukjati D, Reberšek S, Miklavčič D. A reliable method of determining wound healing rate. Medical & Biological Engineering & Computing [Internet]. 2001Mar;39(2):263–71. Available from: <https://doi.org/10.1007%2Fbf02344811>

12. Team ICG. Type 2 Diabetes in Adults: Management. 2015;(28).

13. Control Cfor D, Prevention. Adult Tobacco Use Information - Glossary. r̆lhttps://www.cdc.gov/nchs/nhis/tobacco/tobacco\_glo ssary.htm; 2017.