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A randomized controlled trial comparing EUSOL versus antibiotic loaded collagen granules as dressing agents in the management of traumatic infected wounds

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Abstract
Background: Traumatic wounds are common cause of morbidity in Orthopaedic patients. There can be associated injury to various vital structures i.e bones, muscles, tendons, nerves and vessels. Despite recent advances in wound care, the challenge of managing chronic wounds remains compounded by a lack of consensus on clearly defined wound care principles.
Methods: A randomised controlled trial was used to enrol 130 patients, out of which 65 underwent EUSOL dressing and 65 underwent collagen granules dressing, all the cases were admitted in Orthopaedics ward and were only discharge at the end of treatment or study period whichever was earlier, so there was no loss to follow up. Assessment of wound was done every week for a period of 4 weeks in terms of slough, discharge, granulation tissue, outcome and coverage.
Results: Discharge from the wound was found to be lesser in collagen granules group and by the end of 3rd and 4th week it was significantly lesser in collagen granules group (P value <0.05). Floor area covered with slough were lesser in collagen granules group, as early as 1st week (P value <0.05). Healthy granulation tissue, final outcome and coverage appeared earlier with collagen granules group. P value<0.05 by the end of 2nd and 3rd week. Total cost of therapy was less and patient compliance was better with collagen granules group.
Conclusion: Antibiotic loaded collagen granules showed better results in terms of discharge, granulation tissue, healing, duration and cost of therapy, patient compliance and acceptability.

Keywords: wounds, EUSOL, collagen granules, dressing

Introduction
Traumatic wounds are common cause of morbidity in Orthopaedic patients. There can be associated injury to various vital structures i.e bones, muscles, tendons, nerves and vessels. Edinburgh University Solution of Lime (EUSOL) is a standard dressing material used to remove slough and kill bacteria, an essential component of wound healing, but it also damages the granulation tissue thus delaying the healing process [1, 2].
EUSOL is a solution of calcium hypochlorite containing not less than 0.25% w/v of available chlorine buffered with boric acid to a pH of 7.5 - 8.5. Hypochlorite solutions have been known for over two hundred years. *Eau de Javalle* a solution of potassium hypochlorite was first used as a bleaching agent in 1782 and a solution of sodium hypochlorite known as *Eau de Labbaraque* was used as a disinfectant as early as 1820 [4, 5].
Hypochlorite solutions even at very low concentrations have marked inhibitory effect on enzyme systems and because they react with all forms of protein, they are rapidly inactivated by the presence of pus, serum or any other organic matter. For this reason, solutions of hypochlorite used in wound management are sometimes buffered so as to reduce their irritant effect and achieve a compromise between effective biological activity and chemical stability [4].
Proteins are natural polymers and make up almost 15% of the human body. Collagen is the major protein of the extracellular matrix and is the most abundant protein found in mammals, comprising 25% of the total protein and 70% to 80% of skin (dry weight) [7]. Collagen acts as a structural scaffold in tissues, it is now evident that collagen and collagen-derived fragments

control many cellular functions, including cell shape and differentiation, migration, and synthesis of a number of proteins [8].

Collagen plays a key role in each phase of wound healing. Collagen based dressings have the ability to absorb wound exudates and maintain a moist wound environment and acts as a 'sacrificial substrate' in the wound [2, 9]

Collagen based wound dressings are uniquely suited to address the issue of elevated levels of matrix metallo-proteinases (MMPs) by acting as a 'sacrificial substrate' in the wound. It has also been demonstrated that collagen breakdown products are chemotactic for a variety of cell types required for the formation of granulation tissue. In addition, collagen based dressings have the ability to absorb wound exudates and maintain a moist wound environment [10, 11]

One key component of chronic wounds is an elevated level of matrix metallo-proteinases (MMPs). At elevated levels, MMPs not only degrade non-viable collagen but also viable collagen. In addition, fibroblasts in a chronic wound may not secrete tissue inhibitors of MMPs (TIMPs) at an adequate level to control the activity of MMPs. These events prevent the formation of the scaffold needed for cell migration and ultimately prevent the formation of the extracellular matrix (ECM) and granulation tissue [12].

The microcirculation of the wound bed is a key parameter for improving granulation tissue formation and hence wound healing [13]. A synergistic effect on wound healing has been noted when Mupirocin was added to the Collagen granules and it was found to be an ideal biomaterial for the treatment of surface wounds, burns and foot ulcer [14].

Traditional advanced wound care products tend to address the wound's macro environment, including moist wound environment control, fluid management, and controlled transpiration of wound fluids. The newer class of biomaterials and wound-healing agents, such as collagen and growth factors targets specific defects in the chronic wound environment [15].

Despite recent advances in wound care, the challenge of managing chronic wounds remains compounded by a lack of consensus on clearly defined wound care principles. Many organizations have developed guidelines for the assessment and treatment of wounds. These groups often examine the available literature and compile the findings into a set of guidelines. Because few guidelines have been validated, not every hospital follows the same protocol [16].

Since evidence-based medicine has become the new paradigm, the number of international guidelines for the assessment and treatment of wounds has slowly increased. In other words, without diminishing the importance of the opinion of experts in the field, more solid and large RCTs comparing old to new standards of care are needed [17, 18].

Also, in my hospital where this study was conducted and in a setup of a developing country like Nepal, EUSOL is being commonly used in almost all of the traumatic wounds which requires an update for better patient care and shorter hospital stay and should be cost effective [2].

Till date there is no RCT available in the literature and virtually no such study in Nepal that compares the healing effect of EUSOL and Antibiotic loaded collagen granules as dressing agent.

Methods

The study was conducted in the Department of Orthopaedics, B.P. Koirala Institute of Health Sciences, a tertiary care hospital in Eastern Nepal, over a period of Twelve months from January 2013 to December 2013. A total of 130 patients (65 in each Group) were included in study having infected traumatic wounds on any part of the limbs and postoperative infected wounds presenting during the study period. All of the 130 patients were admitted in ward and were treated accordingly there was no loss to follow up since they were discharged only after the study period or once healed whichever was earlier.

All Patients with infected traumatic wounds on any part of the limbs presenting during the study period and postoperative infected wounds were included in study whereas patients with impaired wound healing potential (e.g. comorbidities-Diabetes, connective tissue disorder, any drugs/disease), wound over insensate/avascular limb and patient not giving written consent to participate in the trial were excluded. Patient were allocated using computer generated excel random number generation technique in two groups.

Group A: Use of EUSOL as dressing agent and was made fresh and used within 15 minutes of preparation and constituting of 12.5 grams of Sodium Hypochlorite (Bleaching Powder) and 12.5 grams of Boric acid in 1 litre of lukewarm water. The EUSOL was supplied by hospital free of cost for all the patients included in the study group.

Group B: Use of Antibiotic loaded collagen granules as dressing agent commercially available antibiotic loaded collagen granules (*COMUPIMET*^{R}, Fourrts Laboratories Private Limited, India) consisting of sterile collagen particles with Mupirocin 2% w/w and Metronidazole 1% w/w was used. The patient had to purchase the *COMUPIMET*^{R}

All wounds were thoroughly debrided of necrotic and non-viable tissue and lavaged with normal saline before dressing and size of the wound were measured. Both the groups underwent alternate day dressing till healing or healthy granulation tissue appeared.

Secondary dressings were done by applying sterile gauze pieces and gauze pads in both the groups. Patients were started with oral antibiotics empirically and if having any systemic features like fever then oral antibiotics were started according to culture and sensitivity report of the wound swab.

Ethical clearance was obtained from Institutional Ethical Review Board (IERB).

The wound area, discharge, percentage of area covered with slough, granulation tissue were measured on days 1, 7, 14, 21 and 28 or till covered completely with healthy granulation tissue whichever was earlier. Calculation of probability of complete healing was done at 7, 14, 21 and 28 days.

The 95% confidence interval for relative-risk and prevented fraction was calculated using Epi-info 6 software (WHO, Geneva) and intervention were tested by appropriate parametric and non-parametric statistical technique (example t-test, z-test, X^2- test etc.) depending upon the nature of the variables in both the groups. Multivariate analysis (regression analysis) were applied to control confounding effect of different variables on dependent variables (i.e. outcome variables). The level of significance was set at $P>0.05$, power of study was 80%. ($\alpha=0.05$, $\beta=0.8$).

Results and Discussion

Traumatic wounds are common cause of morbidity in Orthopaedic patients. Although their management is considered under plastic surgery but in developing countries where such facilities are not well developed they are major challenge that an Orthopaedic trauma surgeon faces daily. The associated soft tissue and bony injuries also play part in healing of wounds and vice versa [2]

This study conducted signifies the importance of choice of dressing agent that can be used in our setup. EUSOL and other hypochlorites have been used in past but questions have always been raised regarding its safety and usefulness [20]. There is still search for an ideal dressing agent but it seems to be impossible as each wound has its own characteristics and requires dressing agent accordingly.

There are numerous studies done on EUSOL and Collagen granules separately but none comparing both of them. So enough literature is not available especially a randomised trial comparing the two agents. This study attempts to fulfil the lacunae of the literature to some extent.

Wound status at the end of 1st week- clearly showing discharge.

3rd week- A healthy granulation tissue with no signs of discharge

EUSOL dressing

Exposed Implant- Post operative Day 5

Exposed Implant- 1st day of Collagen granules dressing.

Collagen granules dressing

The mean age of the patients enrolled in EUSOL group was 35.11±20.63 years and Collagen Granules group was 34.55±19.57 years, majority of the patients were young adults, among all the cases, 44.61% of the cases were between the age group of 15 years to 39 years (Table 1).

Table 1: Demographic profile of patient

Character	Category	Group		P value
		Eusol	Collagen Granules	
Age (years)	Mean±SD	35.11±20.63	34.55±19.57	
Gender	Male	50	45	0.323
	Female	15	20	
Mode of injury	RTA	31	34	0.826
	FALL	14	14	
	CRUSH	20	17	
Haemoglobin (gm/dl)	Mean±SD	10.777±1.79	10.878±1.63	0.924
Serum Albumin (gm/dl)	Mean±SD	5.902±.845	5.954±0.70	0.825
RBS (mg/dl)	Mean±SD	97.75±15.27	95.52±12.64	0.326

Initial debridement was performed in all of the enrolled cases followed by 37.7% cases required second debridement. Only 5 cases (7.69%) in Collagen granules group required more than two debridement as compared to 8 cases (12.3%) requiring more than two debridement in EUSOL group. This was comparable to the Bajaj *et al* [2] where minimum of 2

debridement were required by most of the patients in both the groups (46% in EUSOL group and 42% in Sugar group). Further as described by Smith F *et al* [21] surgical debridement were required to expedite wound healing.

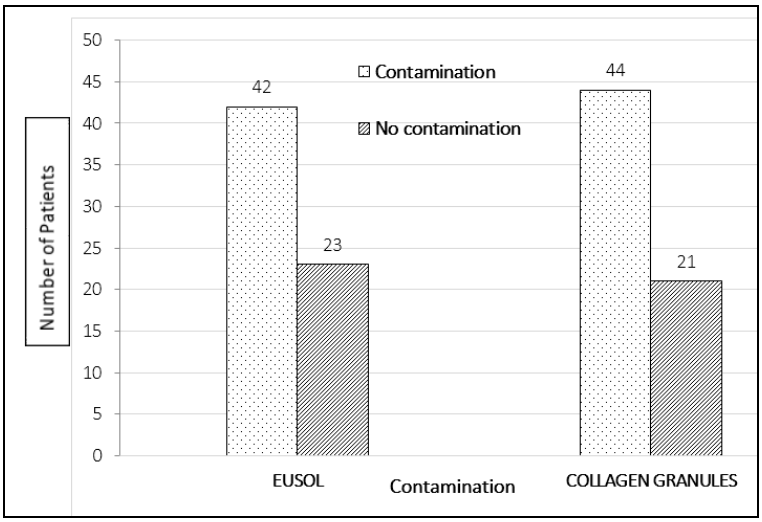

Fig 1: Incidence of contamination

The discharge from the wound of the patients involved in our study improved more significantly in collagen granules group. On 3rd week only 6 cases had serous discharge in collagen group as compared to 16 cases with serous discharge in EUSOL group (Table 2).

The floor area covered with slough showed improved results with collagen granules dressing as compared with EUSOL dressing. Slough was more with collagen granules group in initial 2 weeks but by the end of the 2nd week only 15 cases (23.07%) had slough ranging from 25-50% surface area as compared with EUSOL group where 27 cases (41.53%) had slough. Further the slough decreased significantly with collagen granules dressing as compared to EUSOL dressing on weekly basis

Table 2: comparisons of discharge among the two groups

Discharge		Eusol	Collagen granules	P value
Day 1	Absent	57	52	0.536
	Serous	2	5	
	Purulent	4	4	
	Serosanguineous	2	4	
	Healed	0	0	
Day 7	Absent	30	33	0.203
	Serous	23	27	
	Purulent	9	5	
	Serosanguineous	3	0	
	Healed	0	0	
Day 14	Absent	37	38	0.737
	Serous	18	18	
	Purulent	8	6	
	Serosanguineous	1	0	
	Healed	1	3	
Day 21	Absent	35	36	0.054
	Serous	16	6	
	Purulent	0	0	
	Serosanguineous	0	0	
	Healed	14	23	
Day 28	Absent	34	24	0.240
	Serous	0	1	
	Purulent	0	0	
	Serosanguineous	0	0	
	Healed	36	45	

The healthy granulation tissue was seen at day 7 in 24 cases in collagen granules group as compared to only 13 cases in EUSOL group. Further, significant difference in the quality of granulation tissue was seen in subsequent weeks with collagen granules. Our study was comparable with the study conducted by Vin F *et al* [22] where they found that Collagen accelerated healing in venous leg ulcers with 20% more wound healing (P=0.0797).

Table 3: comparing granulation tissue formation among the group

Granulation Tissue		Eusol	Collagen Granules	P Value
Day 1	Absent	65	65	0.0
	Pale	0	0	
	Pink	0	0	
	Red	0	0	
	Healed	0	0	
Day 7	Absent	52	41	0.015
	Pale	6	19	
	Pink	7	5	
	Red	0	0	
	Healed	0	0	
Day 14	Absent	36	14	0.0
	Pale	16	30	
	Pink	5	18	
	Red	7	0	
	Healed	0	3	
Day 21	Absent	18	11	0.02
	Pale	24	25	
	Pink	8	14	
	Red	1	0	
	Healed	14	15	
Day 28	Absent	0	0	0.416
	Pale	25	2	
	Pink	10	21	
	Red	0	3	
	Healed	35	45	

Subrahmanyam M *et al* [23] also found early granulation tissue and better wound healing property in honey as compared to EUSOL in dressing of Fournier's gangrene. (Table 3)

Patients in both the group showed signs of healing with time. But patients with collagen granules group showed early signs of healing in the form of granulation tissue formation,

epithelialisation. Healthy granulation was seen on 30 (46.15%) cases by day 14 and 38(58.46%) cases by day 21 in collagen granules group as compared to only 9(13.84%) cases in day 14 and 23(35.38%) cases in day 21 in EUSOL group.

Table 4: comparisons of healing among the two groups

		Eusol Group	Collagen granules group	P value
Final outcome at Day 7.	No sign of healing	54	48	0.104
	Sign of healing	11	17	
	Healed	0	0	
Final outcome at Day 14.	No sign of healing	45	22	0.00
	Sign of healing	19	40	
	Healed	1	3	
Final outcome at Day 21.	No sign of healing	24	2	0.00
	Sign of healing	27	40	
	Healed	14	23	
Final outcome at Day 28.	No sign of healing	2	0	0.416
	Sign of healing	33	26	
	Healed	35	39	

It was comparable to the study conducted by Lazaro *et al* [24] in which they found that significantly more wounds achieved complete healing with collagen, 63% versus 15% ($p<0.03$) [25] Mean time to healing was 23.3±9.9 versus 40.6±1.15 days compared to controls ($p<0.01$) (Table 4).

Coverage of the wound was done on 4th week in most of the cases. But coverage was started earlier in collagen granules group, SSG was earliest done on day 7 in collagen granules group in 2 cases whereas none in EUSOL group, further 12 Cases underwent SSG/Flap in Collagen granules group as compared to EUSOL group where only 3 cases underwent SSG by Day 14. Delayed healing was noted in EUSOL group as 31 cases underwent coverage in 4th week as compared to only 20 cases in collagen granules group. Findings of our study was comparable to Ermolov AS *et al* [26] where he compared the wound healing potential and described that Collagen-1-based dressing showed accelerated wound epithelialisation(5-7 days versus 20-22 days with gauge dressing. Further Perumal S *et al* [14] found out that the wound closure analysis revealed complete epithelialisation in 14.2 ± 0.44 days for Mupirocin-SM loaded collagen, whereas this was 17.4 ± 0.44 days and 20.6 ± 0.54 days for collagen and control groups, respectively. Consequently, the synergistic strategy of combining mupirocin-loaded silica microspheres and collagen as a Mu-SM loaded collagen dressing material would be an ideal biomaterial for the treatment of surface wounds, burns and foot ulcers.

Table 5: probability of healing comparing both the groups

Probability of healing	EUSOL	Collagen granules	Odds ratio
1st week	11/65,(0.16)	17/65, (0.26)	1.62
2nd week	19/65, (0.29)	40/65, (0.61)	2.10
3rd week	27/65, (0.41)	40/65, (0.61)	1.48
4th week	33/65, (0.50)	26/65, (0.40)	0.8

Collagen granules are found to 1.5 times better in terms of wound healing on the basis of granulation tissue and epithelialisation and keratinisation as compared to EUSOL (Table 5).

In term of cost to the patient, EUSOL was provided free of cost to the patient as it was prepared fresh in the morning but collagen granules cost around 730 nepalese rupee for a 30gram, looking at the direct cost of the dressing material used collagen granules comes very expensive but indirect cost like shorter hospital stay lesser number of debridement, early healing and better patient compliance collagen granules outweighs the EUSOL in terms of total cost of therapy to the patient.

Conclusion

On the basis of these results my study clearly indicated that collagen granule dressing was better than EUSOL dressing in terms of discharge, slough removal, coverage of wound and healing collagen granules are better dressing agent as compared to EUSOL. Other factors like the influence of bacteria cultured from wound as well as the dressing material itself and cost effectiveness still remain a challenge and require further studies.

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