

ORIGINAL RESEARCH

Efficacy of topical hyaluronic acid with betadine on wound healing compared to betadine alone

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ABSTRACT

Background: To study the efficacy of topical hyaluronic acid with betadine compared to betadine alone.

Materials & methods: A total of 100 subjects were enrolled. They were divided into two groups as test (Hyaluronic acid with betadine group) and control group (Betadine alone group) with 50 in each. Outcome was evaluated. The results were analysed using SPSS software.

Results: A total of 100 subjects were enrolled. 8 subjects (of controls) underwent subsequent limb amputation whereas no patient in case group underwent amputation. Results revealed that wound healing was better in study group adjunct to control, non significant VAS score association and relatively shorter hospital stay was found in study group.

Conclusion: Topical hyaluronic acid with betadine could be considered as an adjunct to betadine in local wound management

Keywords: Wound healing, Hyaluronic acid, Betadine.

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INTRODUCTION

Wound repair is considered one of the most complex biological procedures of our body, and it is divided into four main phases: hemostasis, inflammation, proliferation, and remodelling. ¹ In normal healing, these phases occur in a sequential but overlapped way, and they are completed in a period between three weeks and some months, leading to the formation of scar tissue. ^{2,3} Unfortunately, various complications can occur and affect the damage recovery time required. For instance, bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* can readily colonize wounds, causing aggressive and intricate infections. ⁴ Wound healing is a complex biological process in which events occur in a coordinated and sequential manner involving interactions of various cell types, matrix components, proteases and cytokines. ⁵ Healing by first intention occurs by minimizing the volume of connective tissue deposited, generating minimal scarring and restoring the epithelial barrier against infections. ^{6,7} This kind of lesions affect only the superficial layer of the skin or mucous membranes, presenting a solution of continuity of the tissue, without loss or destruction of it, with slight bleeding, but they are usually extremely painful and do not represent a risk to the victim when isolated. ⁸ Povidone-iodine (Betadine) is an antiseptic solution consisting of polyvinylpyrrolidone with

water, iodide and 1% available iodine; it has bactericidal ability against a large array of pathogens. ⁹ Hyaluronic acid (HA) is an innately occurring high molecular weight polysaccharide formed in the human body as a part of a natural wound healing mechanism. HA acts as an essential element of cell migration and proliferation, thus regulating tissue hydrodynamics. ¹⁰ In addition, it has ideal properties, such as non-immunogenicity and biocompatibility with human oral tissues. The essential cellular interactions of HA, with various mediators, including CD44, a receptor for HA-mediated motility (RHAMM), and intercellular adhesion molecule-1 (ICAM-1), make HA crucial during each stage of wound healing. ¹¹ Moreover, the adjunctive use of HA demonstrated a significant improvement in the periodontal clinical parameters. ^{12,13} Hence, this study was conducted to study the efficacy of topical hyaluronic acid with betadine on comparing to betadine alone.

MATERIALS & METHODS

A total of 100 samples were enrolled. They were divided into two groups as test and control group with 50 in each. Inclusion criteria for the present study included Ulcers over lower limb, Chronic non healing ulcers, Ulcers with comorbidities or Ulcers with impaired vascularity. Subjects in both groups underwent daily wound dressings under strict aseptic

precautions. The test group subjects received topical hyaluronic acid with betadine during dressings and the control group received betadine alone dressing. After 7 days of dressings, the subjects were evaluated. The granulation tissue and discharge was evaluated. The data was analysed using chi-squared test. The results were analysed using SPSS software.

amputation whereas no patient in case group underwent amputation. The rate of granulation tissue formation was significantly faster amongst cases: 95% cases showed granulation at the end of Day 7 as compared with 65% amongst controls. Results revealed that wound healing was better in study group adjunct to control, non significant VAS score association and relatively shorter hospital stay was found in study group.

RESULTS

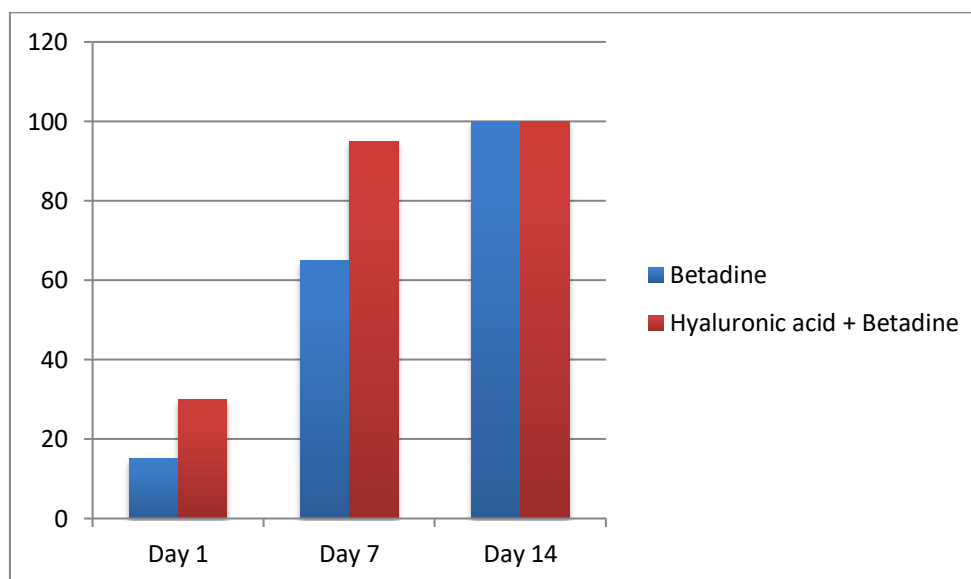
A total of 100 subjects were enrolled. 8 subjects (16%) of controls underwent subsequent limb

Table 1: Amputations in the groups

Group	Yes	No
Betadine dressing	8	42
Hyaluronic acid with acid with betadine dressing	0	50
p- value	0.001 (Significant)	

Table 2: Granulation tissue formation

Days	Percent of subjects with granulation tissue	
	Betadine dressing	Hyaluronic acid + Betadine
Day 1	15	30
Day 7	65	95
Day 14	100	100



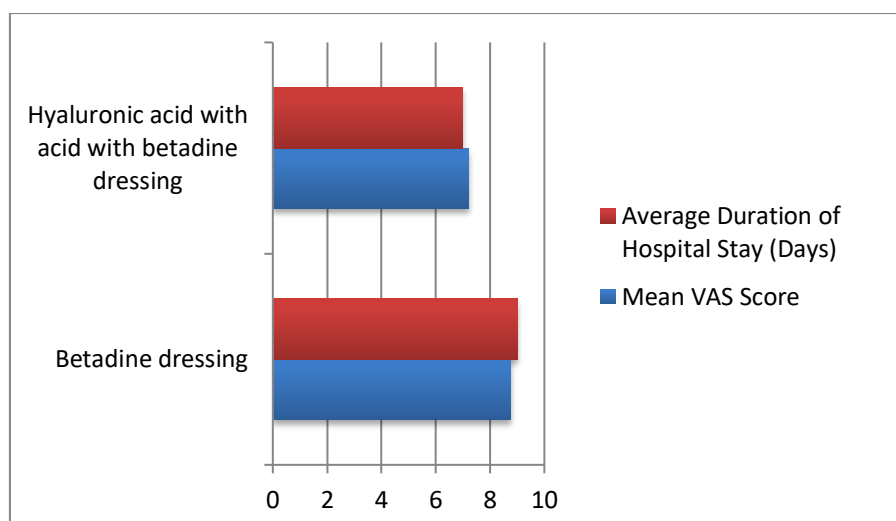
Graph 1: Granulation tissue formation

Table 3: VAS Score

Group	Mean VAS Score
Betadine dressing	8.77
Hyaluronic acid with acid with betadine dressing	7.22
p- value	0.012 (Non Significant)

Table 4: Hospital Stay

Group	Average Duration of Hospital Stay
Betadine dressing	9 days
Hyaluronic acid with acid with betadine dressing	7 days



Graph 2: VAS Score and Hospital Stay

DISCUSSION

The investigations that focused on drug release patterns of HMW and LMW-HA in vitro are limited. The present study is one of the few to evaluate the in vitro release of LMW-HA. Quantification of HMW-HA was difficult due to its high molecular weight and complex molecular structure.¹⁴ The effectiveness of LMW-HA over HMW-HA could be related to its immunoregulatory property, which is usually noticed at the sites of inflammation. LMW-HA is formed from enzymatic degradation of HMW-HA. LMW-HA promotes the production of immune mediators thereby stimulating an immune response. This could enhance wound healing better than the high molecular weight variant.¹⁵ Hence, this study was conducted to study the efficacy of topical hyaluronic acid with betadine on comparing to betadine alone. In the present study, a total of 100 subjects were enrolled. 8 subjects (16%) of controls underwent subsequent limb amputation whereas no patient in case group underwent amputation. A study by Dr. Sudhir S et al, extremity ulcers are amongst the most common surgical presentations in outpatient departments in India, cutting across all strata of society and all regions of India. They are associated with significant morbidity, and sometimes require major amputations, and may occasionally result in mortality as well. It is therefore not unusual that many studies have been conducted in recent times to discover newer methods of local management of extremity ulcers. Many such methods, viz. Vacuum assisted closure, which use the principles of wound healing, are now being employed with good success rates. Nevertheless, many of these methods have the disadvantage of higher costs, which the common man is unable to afford, making it out of reach of those desperately in need of adequate and thorough local management of ulcers.¹⁶ In the present study, the rate of granulation tissue formation was significantly faster amongst cases: 95% cases showed granulation at the end of Day 7 as compared with 65% amongst controls. Another study by Lanka J et al,

Hyaluronic acid (HA) is a naturally occurring biopolymer, with a remarkable wound healing property. Hydrogels of HA and zinc oxide were formulated with carbopol as a carrier. In vitro drug release was performed by UV spectrophotometry, dialysis, and vial bag methods. Cytotoxicity assessment of HA and zinc-oxide gels was performed in human periodontal ligament fibroblasts (HPdLF) and human gingival fibroblasts (hGFs). An inverted phase-contrast microscope was used to assess the morphological changes. At 24 and 48 hr, HPdLF cells showed the highest viability in 0.1% low molecular weight-HA (LMW-HA) with a median value of 131.9, and hGFs showed the highest viability in 5% LMW-HA with a median of 129.56. The highest viability of HPdLF cells was observed in 5% high molecular weight-HA (HMW-HA), with a median value of 127.11. hGFs showed the highest viability in 1% HMW-HA with a median value of 97.99. Both HPdLF and hGF cells showed complete cell morbidity with zinc-oxide hydrogels. Therefore, zinc oxide-based gels in concentrations as low as 9% could be toxic intraorally to soft tissues that harbor gingival and periodontal ligament fibroblasts.¹⁷ Parker and colleagues carried out an RCT of 45 patients undergoing major resection for large bowel carcinoma. The study group consisted of 22 patients with a mean age of 69 years who received preoperative irrigation with 500 mL of 10% aqueous povidone-iodine; the control group consisted of 23 patients with a mean age of 68 years who received an equivalent amount of irrigation with water. All the patients received antibiotics consisting of intravenous ampicillin 500 mg, or erythromycin if allergic to penicillin, and metronidazole 500 mg. Infection was defined as pus discharging from the wound. Only 1 patient (4.5%) in the study group developed wound infection, whereas 9 patients (39.1%) in the control group developed infection ($p < 0.01$). No risks were identified.¹⁸ The main risks associated with povidone-iodine irrigation were primarily related to

thyroid function. Varying findings were reported, but no serious harms occurred. Because contamination of the povidone-iodine solution has been associated with infections, precautions should be taken to ensure its sterility before use.¹⁹ Although not directly relevant to this review, the use of 10% topical povidone-iodine ointment (1% available iodine) in burn patients has resulted in severe metabolic acidosis due to the absorption of iodine or acidic povidone-iodine. Thus care should be taken when using it in patients with burns covering more than 20% of the body surface or when renal failure is present.²⁰

CONCLUSION

The use of topical hyaluronic acid with betadine has been found to have higher rates of granulation tissue formation and more rapid wound healing. Hence, topical hyaluronic acid could be considered as an adjunct to betadine in local wound management.

REFERENCES

- Gurtner G.C., Werner S., Barrandon Y., Longaker M.T. Wound repair and regeneration. *Nature*. 2008;453:314–321.
- Clark R.A. *The Molecular and Cellular Biology of Wound Repair*. Springer Science & Business Media; Cham, Switzerland: 2013.
- Clark R.A.F. Chapter 76—Wound repair: Basic biology to tissue engineering a2—Lanza, robert. In: Langer R., Vacanti J., editors. *Principles of Tissue Engineering*. 4th ed. Academic Press; Boston, MA, USA: 2014. pp. 1595–1617.
- Fazli M., Bjarnsholt T., Kirketerp-Møller K., Jørgensen B., Andersen A.S., Kroghfelt K.A., Givskov M., Tolker-Nielsen T. Nonrandom distribution of pseudomonas aeruginosa and staphylococcus aureus in chronic wounds. *J. Clin. Microbiol.* 2009;47:4084–4089.
- Sinno H., Prakash S. Complements and the wound healing cascade: an updated review. *Plast Surg Int*. 2013;2013:146764.
- Baranoski S., Ayello E.A. first ed. Lippincott Williams & Wilkins; Pennsylvania: 2004. *Wound Care Essentials*.
- Wlaschin K.F., Ninkovic J., Griesgraber G.W. The impact of first-aid dressing design on healing of porcine partial thickness wounds. *Wound Repair Regen*. 2019;27(6):622–633.
- Gefen A., Ousey K. Update to device-related pressure ulcers: SECURE prevention. COVID-19, face masks and skin damage. *J. Wound Care*. 2020;29(5):245–259.
- Zamora JL. Chemical and microbiologic characteristics and toxicity of povidone-iodine solutions. *Am J Surg* 1986;151:400-6.
- Moseley R, Waddington RJ, Embery G. Hyaluronan and its potential role in periodontal healing. *Dental Update*. 2002. Apr 2;29(3):144–148.
- Manzanares D, Monzon ME, Savani RC, et al. Apical oxidative hyaluronan degradation stimulates airway ciliary beating via RHAMM and RON. *Am J Respir Cell Mol Biol*. 2007. Aug;37(2):160–168.
- Pagnacco A, Vangelisti R, Erra C, et al. Double-blind clinical trial vs. placebo of a new sodium-hyaluronate-based gingival gel. *Attualita Terapeutica Internazionale*. 1997;15:1–7.
- Engström PE, Shi XQ, Tronje G, et al. The effect of hyaluronan on bone and soft tissue and immune response in wound healing. *J Periodontol*. 2001. Sep;72(9):1192–1200.
- Falcone SJ, Palmeri DM, Berg RA. Rheological and cohesive properties of hyaluronic acid. *J Biomed Mater Res A*. 2006. Mar 15;76(4):721–728.
- Monasterio G, Guevara J, Ibarra JP, et al. Immunostimulatory activity of low-molecular-weight hyaluronan on dendritic cells stimulated with aggregatibacter actinomycetemcomitans or porphyromonas gingivalis. *Clin Oral Investig*. 2019. Apr;23(4):1887–1894.
- Dr. Sudhir S, Dr. Harish Kumar P, Deepak R Sridhar, Dr. Nagaraja Pruthvika. To study the efficacy of topical hyaluronic acid on wound healing compared to betadine by bates Jensen wound assessment tool. *Int J Surg Sci* 2021;5(4):17-22.
- Lanka J, Kumar S, B MK, Rao S, Gadag S, Nayak UY. Drug Release and Cytotoxicity of Hyaluronic Acid and Zinc Oxide Gels, An In-Vitro Study. *Des Monomers Polym*. 2022 Jul 24;25(1):212-219.
- Parker MC, Ashby EC, Nicholls MW, et al. Povidone-iodine bowel irrigation before resection of colorectal carcinoma. *Ann R Coll Surg Engl* 1985;67:227-8.
- Panlilio AL, Beck-Sague CM, Siegel JD, et al. Infections and pseudo-infections due to povidone-iodine solution contaminated with Pseudomonas cepacia. *Clin Infect Dis* 1992;14:1078-83.
- Pietsch J, Meakins JL. Complications of povidone-iodine absorption in topically treated burn patients. *Lancet* 1976;1:280-2.