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ORIGINAL

A Clinical Study on the Use of EGF-CMC Hydrogel in Minimizing Biofilm Formation in Diabetic Wounds: Implications for Preventing Marjolin's Ulcer and Associated Cancer Risk

Estudio clínico sobre el uso del hidrogel EGF-CMC para minimizar la formación de biopelículas en heridas diabéticas: Implicaciones para la prevención de la úlcera de Marjolin y el riesgo de cáncer asociado

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ABSTRACT

Introduction: Diabetes-related wounds are worsened by slowed healing and heightened bio-film formation vulnerability, which can result in chronic infections. Epidermal growth factor (EGF) is well known for having regenerating qualities, therefore adding the carboxy-methyl cellulose (CMC) were the hydro gel in preventing the growth of bio films in wounds caused by diabetes.
Method: a 13-week placebo-controlled clinical research with 30 type 2 diabetes patients (17 using CMC hydrogel, 13 using EGF-CMC hydrogel) assessed wound healing in venous ulcers. Swab samples were taken at weeks 2, 7, and 13. Microbiologists and imaging techniques analyzed biofilm formation, microbial load, strain identification, and pathogenic gene expression.
Result: comparing the EGF-CMC a hydrogel to the untreated category, a significant reduction in bio film formation was observed. Reduced numbers of microbes were found by microbiology examination and imaging procedures verified the reduction of the bio film formations. This emerged that the likelihood of separating organisms that produce bio films of injuries given CMC hydrogel formulation were eighty-three percent higher than that from injuries handled with EGF-CMC.
Conclusion: the research indicates that isolates with decreased formation of bio film were seen in lesions that received EGF-CMC hydrogel, which is despite the fact of no discernible differences in bacterium counts or genes related to virulence could be identified. This result emphasizes how the reactive covering can affect the bacteria activity in diabetes patients' persistent injuries.

Keywords*:* Epidermal Growth Factor; Carboxy Methyl Cellulose; Diabetic; Bio-Film Formation; Wounds.

RESUMEN

Introducción: las heridas relacionadas con la diabetes se ven agravadas por una cicatrización más lenta y una

mayor vulnerabilidad a la formación de biopelículas, lo que puede dar lugar a infecciones crónicas. El factor de crecimiento epidérmico (EGF) es bien conocido por tener cualidades regeneradoras, por lo que la adición de carboximetilcelulosa (CMC) fue el hidrogel en la prevención del crecimiento de biopelículas en heridas causadas por la diabetes.
Método: en una investigación clínica controlada con placebo de 13 semanas de duración con 30 pacientes con diabetes de tipo 2 (17 con hidrogel de CMC y 13 con hidrogel de EGF-CMC) se evaluó la cicatrización de heridas en úlceras venosas. Se tomaron muestras de frotis en las semanas 2, 7 y 13. Los microbiólogos y las técnicas de imagen analizaron la formación de biopelículas, la carga microbiana, la identificación de cepas y la expresión de genes patógenos.
Resultado: al comparar el hidrogel EGF-CMC a con la categoría no tratada, se observó una reducción significativa de la formación de biopelículas. La reducción del número de microbios se constató mediante examen microbiológico y los procedimientos de imagen verificaron la reducción de las formaciones de biopelícula. Esto puso de manifiesto que la probabilidad de separar los organismos que producen biopelículas de las lesiones a las que se administró la formulación de hidrogel CMC era un ochenta y tres por ciento superior a la de las lesiones tratadas con EGF-CMC.
Conclusión: la investigación indica que se observaron aislados con menor formación de biopelícula en las lesiones que recibieron el hidrogel EGF-CMC, a pesar de que no se pudieron identificar diferencias perceptibles en el recuento de bacterias ni en los genes relacionados con la virulencia. Este resultado pone de relieve cómo el recubrimiento reactivo puede afectar a la actividad bacteriana en las lesiones persistentes de los pacientes diabéticos.

Palabras clave: Factor de Crecimiento Epidérmico; Carboximetilcelulosa; Diabéticos; Formación De Biopelícula; Heridas.

INTRODUCTION

Epidermal growth factor (EGF) is a kind of protein which has been essential to the development, survival and repair of the cells. This serves as a signaling molecule which encourages the continued existence, distinction and multiplication of the cells. A distinct and complex difficulty is in the medical field. Because of the weakened and complicated milieu around these injuries, a customized strategy is necessary to meet the unique features of individuals with diabetes. The effectiveness of wounds care, especially using therapies that involve EGF Cross-Linked CMC hydro gel, could possibly be compromised if it is unable to adjust to the changing needs of wounds caused by diabetics. It is critical to comprehend the nuances of wounds caused by diabetes and devise plans to increase the flexibility of wound care treatments to provide patients with superior treatments and outcomes. Fundamentally the EGF acts by attaching to the receptor for EGF to corresponding receptors and starting series of the biochemical reactions that change the functioning of genes and the activity for the cells. It has demonstrated promise as a substance for the medical management of wounds caused by diabetes. The small scale environment in wounds sustained by diabetes tends decreased the growth of tissues. Since EGF is essential for both cell division and expansion, it can be able to remove these specific barriers.[1]

EGF plays an extensive function that it goes through outside by controlling the cells development; this plays a part on healing from injuries, immunity oversight and the tissue equilibrium management. A more complex depiction of the complex network of molecules that the EGF orchestrates begins to take shape. This new perspective clarifies the protein's possible medicinal uses as well as its importance in comprehending the workings of cells.[2]

The basic features of the EGF providing an insight toward their molecule subtleties as well as the extensive effects of it functions inside the complex web of cells. Carboxy methyl cellulose (CMC) is a popular and adaptable polymer this is because of its special qualities finding employment across an array of the sectors. The organic polymeric a material called the CMC which is present in the cells of plants that provides the source for that dissolved in the water viscose derivatives. The small size around injuries in diabetics is vulnerable to harm and problems, which creates the perfect environment for the growth of bio films. Bio films raise the possibility of persistent germs, delaying closing of wounds and other broader issues in addition to impeding the normal therapeutic cascades. Therefore, it is essential that tackle the problem of bio film development in wounds caused by diabetics to treat wounds. CMC units are added in the viscose substrate for enhancing its capability to dissolve as well as to give it maximizes the expanding, recovering and emulsification of the qualities.[3]

The CMC is establishing its place as a vital component across a number of sectors including beverages along with food, medication, beauty products as well as fabric toward its capacity to generate translucent gels and persistent formulations. Polymers that are hydrophilic arranged into a dynamic multidimensional structure that can hold significant quantities of liquid demonstrate great promise for solutions for a range of biological uses.[4]

Hydro gels have the water content that are biocompatible and have physical characteristics that can be adjusted, which makes them ideal over a variety of rehabilitative combined with medicinal applications. These films are a significant problem in clinical and the commercial environments because it is made up of the bacteria enclosed in a matrix of cells that manufacture. An impact on the deterioration of factories, the recurrence of recurring illnesses and the contamination of healthcare devices. Therefore, it is crucial to address the controlling and avoiding the spread of bio films creation. The function of hydro gels among the circumstance that illuminates impedes the formation of bio films to provide details in the mechanisms.[5]

The objective of the research is to reduce or prevent the bio films formations in diabetic wound and encouraging the healing process of wounds as well as shielding with diabetes from problems brought by the growth about bio films. To discover the diabetes related sores and leg sores continue to be serious medical conditions and their consequent higher medical load was caused by the accompanying medical expenses. Diabetic was a meticulously orchestrated series of actions that make up the wound-closure procedure.[6]

The explored that the CMC was the wonderful qualities of polymeric dressings for wounds substances, like as their cell's resemblance, biocompatibility ability to break down the affordability and non-toxicity, make them extremely popular. It was utilized in many different pharmacological and biological industries. Because of its hydrophobic properties CMC can be combined and cross linked with a variety of substances, including inorganic in nature made up and organic polymer substances, to create new biological materials for wound care.[7]

The long-term wounds are dangerous complications linked to the condition that are hard to cure because of elevated sugar, cellular damage and bacterial infections linked to bio films. Medications cannot enter the cell wall of bacterial films due to its complicated structures, rendering standard antibiotics unsuitable in clinical applications. These highlight the urgency to identify alternative therapies that were more secure to lower the incidence of microbiological bio films related persistent wound related infections. Inhibiting bio films creation with an organic macromolecule based nano delivery technology offered a novel method to solve such problems.[8]

The diabetes sufferer's injuries, particularly Marjolin ulcers may also form from osteomyelitic lesions and, rarely, in the foot, were harder to recover from than non-diabetic lesions and can rapidly worsen, necessitating surgery. Diabetes injuries were unable to heal or it's numerous effects controlled by standard therapies. It was discovered that development variables play a vital role in controlling the complicated wound repair process in diabetics.[9]

To development factors, including blood vessel endothelial growth factor, insulin like development element, particularly transforming growth factor beta 1, have distinct functions in the recuperation of wounds from diabetes. The suggested which medical care of wounds from diabetes can be enhanced by an approach to therapy that modulates various growth factors to promote the healing process.[10]

To determined that the sessile in nature populations of microbes, predominantly microbes, which develop on both abiotic as well as biotic substrates, have been identified as bio films that were formed. The extrinsic material made of polymers which encases the microbes offers improved defense against antibiotics. Bio films creation is most suited to persistent injuries. A lack of a weakened host's defense, microbes could adhere to wound related detritus and spread across the wounds. To formulating techniques and distribution methods used to remove or distribute microfilms, successfully addressing both acute as well as ongoing wounds.[11]

The billions of individuals worldwide have insufficient healing of wounds that has been connected to greater fatalities and more expensive healthcare. The latest research has shown that the use of materials made from living organisms affected the recovery of wounds. With limiting the spread of infectious agents, reducing swelling and promoting angiogenesis, which organic substances in the injury's microcosm were able to trigger a variety of molecular and the cellular mechanisms which could promote recuperation that possibly transform an unsealing the atmosphere into a condition capable of suitably rehabilitation. Its purpose was to give a general review to the pathogenesis and mechanics behind healing wounds.[12]

To discovered that the creation of blister healing goods like lotions and dressings for wounds hydro gels by tiny particles and bio films as especially nanotechnology incorporating chitin polymers was attracting interest potential small or nanotechnology. Chitosan's antibacterial properties, breakdown and survival are key drivers towards these purposes.[13]

The treatment especially persistent lesions that were contaminated like an ulcer caused by diabetes was harder especially for individual's defenses were compromised. Additionally, due to the fact that harmful microbes and fungal organisms were developing immunity to antibiotics, treating microbiological diseases at the area of injury with currently prescribed medicines could prove to be successful.[14]

The prevalent kinds for persistent injuries include ulcers resulting from pressure, vein, artery blisters and ulcers caused by diabetes. According to the present diabetes and overweight epidemics as well as the growing number of senior persons in the community, which has become more susceptible to persistent injuries then individuals their age, the financial cost on long term injuries remains increasing. Additionally, opportunism and medication antibiotic resistant organisms were capable of causing devastating diseases in this group of people.[15]

To determined that the growth of hormones, inflammatory substances and various kinds of cells must coordinate throughout the complex procedure of wound recovery to be able to turn a serious lesion into a healed scarring. Long lasting injuries and scarred diseases were of repair difficulties that pose significant risks to health and it were associated with the deregulation pertaining to significant inflammatory mediators at various stages of recovery. The present form of therapy in these types of diseases was indiscriminate and ineffectual, while encouraging preliminary findings, biologic therapies that aim at restoring the equilibrium of developmental factors or cytokines to the wounds were not having favorable results in clinical trials.[16]

The breakdown by nature and interaction within the biological milieus, hydro gels as well, were complex dimensional polymers frameworks. These systems present themselves as feasible and attractive platforms for many medicinal applications. This was clearly shown that using hydro gels throughout research was practically feasible. Healing injuries is one of the major biological applications of fluids that were commonly used.[17]

METHOD

Data collection

For simplicity, the research population comprised 30 diabetes type 2 people who had vascular or ulcers in their feet (the EGF CMC group with 13 in the CMC category as well as 17 in). In a 1:1 split, all 30 patients were randomized as group 1 (G1) and group (G2). The randomizing number has been used throughout the patient's enrollment process and it was produced using the SPSS program. There were no financial losses throughout the monitoring phase following randomized. During the course of the research, the team's allocation remained a secret from the team of statistics and those participating before the principal assessment completed.

Procedures in research

Following an inpatient approach previously reported, registered individuals had week clinical tests administered by nurses with certification throughout the three months monitoring phase. Pair research caregivers took measurements of the fluid from wounds utilizing Levine's brush cultures method. A Weekly 2 (S2) and weekly 7 (S7) saw the collection of biological specimens, which were shipped to a facility over microbiological analysis.

Detection of S. aureus and p. aeruginosa and tested for Antibiotic Being susceptible

After being collected, samples were placed in two milliliters of sterile water (0,9 % NaCl), submerged in Stewart transporting media and swirled. Then, a millimeter of that solution was incorporated into the same amount of trypticase soybean broth (TSB) that had been strained repeatedly. The resulting blend was incubated for duration of between twenty-four and forty-eight hours at 35 degrees Celsius. This procedure made it easier for the microbiological material found in the swab scraps to establish and be cultured, which helped with the investigation's later analysis.

Quantitative Strategies for Antimicrobial Identification among Polymerase Chain Reaction in Real Time

Quantitative strategies for antimicrobial identification among polymerase chain reaction in real time in S. aureus and P. aeruginosa by using specific to species markers created using DNA taken out from microbial cultures that were taken straight out of clinical injury samples. The Wizard®® DNA Genome Purity Kits has been used during the purpose of the DNA removal procedure. It was utilized throughout the investigation for accurate bacterial identification. Extraction of DNA was performed on swab specimens that were earlier captured from diabetes participants' persistent injuries that had been administered. By using certain primer which seeks out relevant bacterial DNA made it possible to determine the amounts of microorganisms present. The chemical method contributed to a thorough knowledge of the treatment's effect on bacterial growth in persistent injuries by offering statistical data on the number for P. aeruginosa and Staphylococcus aureus in the wound.

Capability in biofilm formations

During a whole day, each strain had been grown in TSB after being inoculation. A 96 effectively polycarbonate spectrophotometer had been filled with a hundred milliliters from every dilution cultures that had been mixed 1:100 in TSB. The spectrophotometers were placed into incubation to feed a full day. Subsequently, every wells component was sterilized on three occasions using 100 micro liters of saline with phosphate buffer (PBS; pH 7,4). The normal temperature was used to dry the micro plates that received 100 micro liters of 0,1 % of the total purple crystals, as well as the tiny plate was allowed to sit at ambient temperatures approximately fifteen minutes. After the pigment had been taken out, one hundred milliliters of PBS had to be used to clean every well three separate times. After conventional drying, two hundred milliliters containing 95 percent ethanol was applied onto the small plates. With an angle of 570 nm (OD570), spectroscopies were employed for determining the amount of light absorbed. Whenever a strain's OD570 level was higher than that of one of the pair of control

species, it was deemed to be the bio films generator. Standard isolates exhibiting successful bio films creation included P. aeruginosa ATCC 27853 and Staphylococcus epidermal ATCC 12228.

Examining the virulence genes

By examining virulence genes, the investigate delves deeper the cellular characteristics of bacterial pathogenesis. Utilizing certain the primers themselves, the DNA recovered from isolates of both organisms has been analyzed. Using the method of PCR, virulence genes that are linked to toxicity and creation of bio films are identified. Evaluating the possible influence of these genetic variants on the hazardous actions of bacterial populating long-term wounds in people with diabetes was made easier by the findings, which offered insightful information on whether there were any or neglect of virulence related variables. To explore the possible influence of EGF on microbial actions, in vitro studies are carried out to evaluate its disruption of development of bacteria and bio films creation. Typical wounds infectious agents, like Staphylococcus aureus and the bacterium Pseudomonas had been grown in conditions consisting of different EGF injections. The findings demonstrated that EGF could avert the development of such infectious agents by having a dose related inhibiting impact on the proliferation of bacteria. Moreover, there was a significant decrease in bio films formation as a critical component of persistent wounds infections when EGF remained present.

RESULT

Overall, 30 patients were analyzed in the research: whereas EGF with 17 and CMC groups by13.

Sensitivity to antibiotics

The examination of P. aeruginosa colonies' antimicrobial resistance, none among the samples collected by the CMC sample shown tolerance to any particular medication; instead, each strain examined was susceptible to every drug. Conversely, two types of bacteria that were derived from lesions that had been soothed with EGF CMC the hydro gel exhibited no less than an antibiotic tolerance. A type of bacteria proved to be immune to both an antibiotic and aztreonam, while another type was deemed resistant to multiple drugs due to its susceptibility to all antimicrobials evaluated including a number of antibiotic the use of gent imipenem is meropenem this medication and piperacillin with this antibiotic, alongside the exception of polymer B. The inhibitory frequency cannot be different among the two therapy categories.

Microbial load

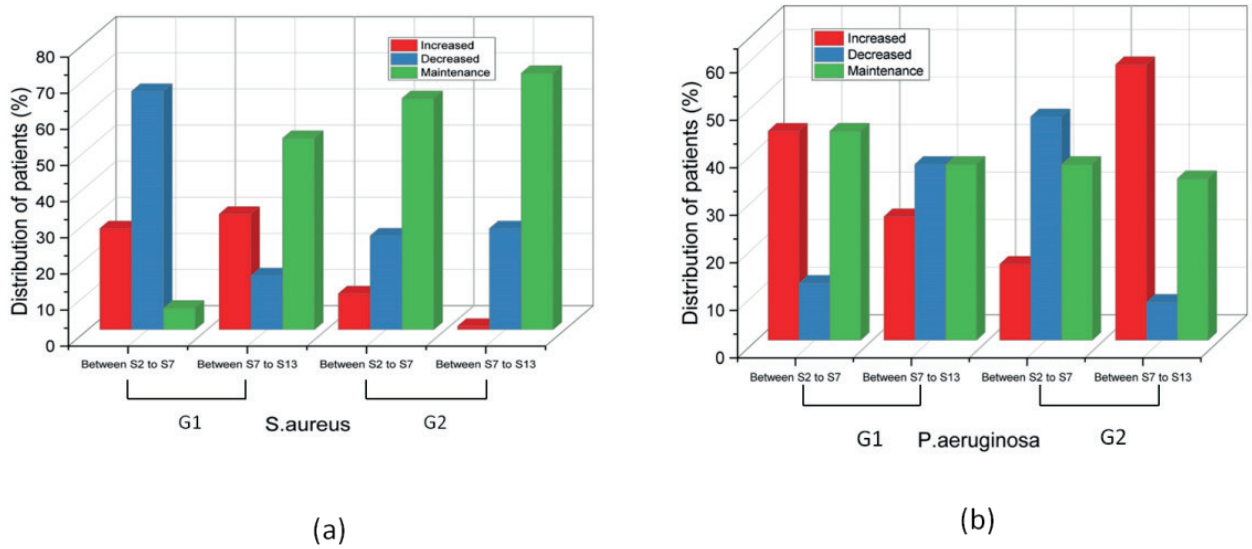

Figure 1. Allocation of patients

Allocations of patients according to bacterial load with the week (S). With regard to P. aeruginosa, individuals receiving EGF had a greater reduction in bacteria burden between S7 and S13 (37 %) compared to S2 and S7 (12 %). Conversely, the higher bacterial burden during S1 and S6 (44 %) was greater than that between S7 and S13 (26 %). During S2 and S7, there was a no shift in the incidence of either a higher or kept microbial loading; therefore, 44 % of the participants had an increase in their bacterial load throughout the duration of the research and an additional 44 percent had a preservation of the loads. Therefore, it is possible to conclude that during the initial period of therapy, the administration of EGF in vivo mostly raised or sustained the P. aeruginosa bacterium burden. The frequency of a lower P. aeruginosa loads varied more among S2 and S7

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(47 %) than between S7 and S13 (8 %), using respect to individuals receiving CMC gels. The length of survival remained unchanged in the P. aeruginosa loads across measurement intervals, with 37 % occurring during S2 and S7 alongside S7 and S13. However, compared to S2 and S7, there was nevertheless a greater incidence of an expanded count of bacteria (58 %) among S7 and S13, suggesting that P. aeruginosa's microbiological burden rose thereafter in vivo in participants receiving CMC treatment. When both treatment groupings were compared it was shown that those who were received CMC hydro gel had a higher incidence of a reduction of the P. aeruginosa microbe load, primarily during S2 and S7 (47 %). Individuals administered using an EGF containing gel had a greater reduction in the S. aureus infections loading; these reductions were most noticeable during S2 and S7 (66 %) as shown in (figure 1 and table 1).

Table 1. Numerical value of distribution of patients in P.aeruginosa

	Categorise	Duration	Increased (%)	Decreased (%)	Maintenance (%)
P.Aeruginosa	Group 1	Between S2 to S7	44	12	44
		Between S7 to S13	26	37	37
	Group 2	Between S2 to S7	16	47	37
		Between S7 to S13	58	8	34
S.aureus	Group 1	Between S2 to S7	28	66	6
		Between S7 to S13	32	15	53
	Group 2	Between S2 to S7	10	26	64
		Between S7 to S13	1	28	71

EGF Interaction with Bacterial Development along with Biofilm Creation

EGF has been demonstrated to have a substantial stimulatory effect on P. aeruginosa development and a moderate lowering effect on S. aureus growth in the in vitro investigation of its effects on P. aeruginosa and S. aureus cultured. The impact of EGF on the ability of S. aureus to produce biofilms was shown to be more significant, as EGF decreased the bacterial transcriptional ability. The generation of P. aeruginosa bio films was not affected by the addition of EGF. The aforementioned findings point to a particular to a species response to EGF, demonstrating unique impacts on P. aeruginosa and S. aureus's in vitro developmental and biomass forming capacities. (Figure 2) represents the spectroscopy was used to evaluate the development of pneumonia aeruginosa and Staphylococcus aureus in vitro at a wavelength of 570 nm optical density evaluated at 570 millimeters (OD570) and (figure 3 and table 2) illustrates the optical density evaluated at 570 millimeters.

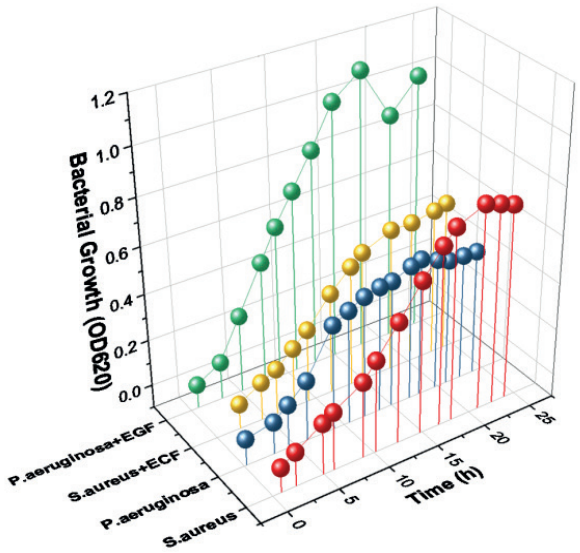

Figure 2. Development of biofilms

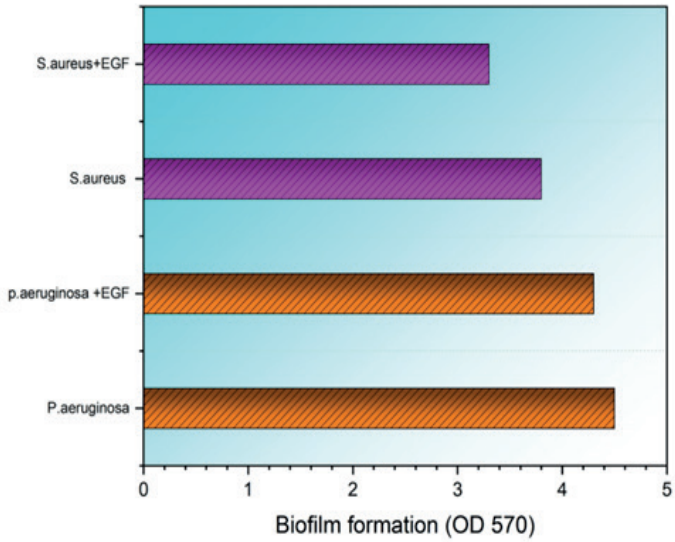

Figure 3. Improvement of biofilms according to the spectrophotometry

Table 2. Numerical analysis of spectrophotometry in the biofilms

Spectrophotometry	Biofilm formation (OD 570)
p.aeruginosa +EGF	4,3
P.aeruginosa	4,5
S.aureus+EGF	3,3
S.aureus	3,8

CONCLUSION

The majority of those with diabetes have persistent injuries that are covered in the bio films made of P. aeruginosa and Staphylococcus aureus, respectively and the management of those microbes is essential to the recovery process. In injuries of people with diabetes who were handled by a two percent the EGF CMC hydro gel the kinds handled in a two percent CMC hydrogel this randomized clinical research sought to assess the growth and creation of bio films of Staphylococcus aureus and P. aeruginosa on wounds. When contrasted with the CMC hydro gel, EGF CMC did not enhance S. aureus as well as P. aeruginosa type strains or pathogenic burdens were isolated among the Staphylococcus aureus and P. aeruginosa which were collected through CMC hydro gel treatment wounds were occupied throughout time after that is injected using EGF CMC showed lower bio films development compared to control isolated.

Limitations and future scope

The microcosm around wounds associated with diabetes is damaged and complicated. The efficacy in EGF CMC hydro gel can become limited if it is unable to adjust to the changing circumstances with wounds from diabetes. Establish a strict wounds management program that includes regular evaluations regarding any kind of sign of progress or regression. Continually modify the treatment approach in light of the documented advancement. Integrate several wound-related treatments, including improved coverings, removal methods and evacuation approaches. This capacity improves the treatment's ultimate efficacy despite with the difficult situation of injuries brought by diabetic.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Formal analysis: Piyush Dadarao Wagh, Ravindra HN, Swayamsidha Mangaraj, Shikhar Ganjoo, Prakriti Kapoor, Manish Nagpal.

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