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SYSTEMIC REVIEW

Hydrogels for Wound Dressing Applications - A Systematic Review

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ABSTRACT

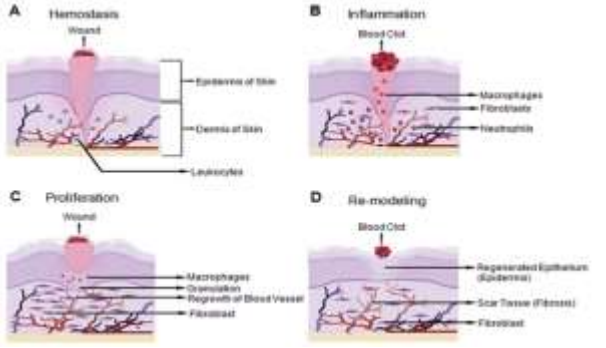
Aim: To discuss the currently available hydrogel wound dressings and their clinical effectiveness.
Method: PubMed/Medline, HEC Digital Library, Wiley Online Library, Wolter Kluwer, Elsevier, and Google Scholar from the year 2013 to 2021 were searched to identify relevant clinical trials and studies.
Results: Forty-three studies that assessed hydrogel vs. non-hydrogel dressings were identified. Compared to the latter, hydrogel dressings associated with a significantly shortened healing time of degree II burn (superficial and deep) wounds, diabetic foot ulcers, traumatic skin injuries, radioactive skin injuries, dog bites, and body surface ulcers. In addition, hydrogel dressing obviously increased the cure rate of diabetic foot ulcers, surgical wounds, dog bites, and body surface ulcers. Moreover, hydrogel dressing significantly relieved pain in degree II burn (superficial and deep) wounds, traumatic skin injuries and laser treatment-induced wounds. However, no significant differences obtained between hydrogel and non-hydrogel dressings in the healing time of surgical wounds, the cure rate of inpatients' pressure ulcers, and phlebitis ulcers.
Conclusion: This comprehensive systematic review of the available evidence reveals that the application of hydrogel dressings advances the healing of various wound types and effectively alleviates the pain with no severe adverse reactions. These results strongly indicate that hydrogel products are effective and safe in wound management.
Keywords: Hydrogels, wound dressing, surgical wounds, diabetic ulcer, burns.

INTRODUCTION

Skin is one of the principal organs which save the human body from tough external atmosphere. There are numerous ways the skin may get injured including burns, ulcers, and trauma. These injuries may lead to a problem in protective barrier capacity of skin. Also, the sensory perception function may be affected[1]. In the United States, the healthcare bears an estimated cost of approximately $50 billion from non-healing wound repair[2,3]. The elderly and the patients suffering from diabetes and genetic disorders are more disposed to abnormal wound healing resulting in continuing problems[4].

Wound healing consists of a series of cellular and molecular events. Wound healing process starts with a tissue injury and ends up in establishing a barrier between the external atmosphere and body[4]. Different phases of wound healing have been identified. These consist mainly of haemostasis, inflammation, proliferation, and remodelling[5]. Different cell types are involved in these wound healing phases. These cells and biomolecules play a critical function in wound healing process. The most effective treatment method is related to the stage of healing process[6].

Figure 1: Stages of wound healing[6]



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Types of Skin Wounds: Skin wounds are classified based on the duration of the healing stages named as non-chronic and chronic wounds. A delay in any of the healing stages causes wounds to become chronic resulting in a non-healing wound. Mainly these problems take place during inflammatory phase. Diabetic, pressure and vascular ulcers are common types of non-healing wounds[6].

Wound dressings: Wound dressings are done to facilitate and optimize wound healing process[1]. The characteristics of an ideal wound dressing are that it should be able to i) maintain an adequate amount of moisture in the wound while removing excess amount of fluid and exudates ii) allow the exchange of gases iii) protect against the micro-organisms causing infection iv) act as a barrier to external physical trauma v) easily removable or biodegradable avoiding any harm to the freshhealing tissue vi) the cells at the wound site be kept viable or prevention from tissue necrosis vii) provide relief from pain and viii) economical[2]. Research on various varieties of wound dressings is available, however the depth of wound and the amount of exudate in the wound dictates the type of dressing to be used. Different types of wound dressings[3]. Commonly used wound dressings are discussed below.

Films: Films are used for wound dressing, as they are made up of polymeric material in thin layers that is transparent. Act as barrier to external environment, thereby holding moisture in the wound. Modifications in films help to gain various behaviors such as adherence, gas permeability and antiseptic. Nevertheless, removing them may harm the keratinocytes at the healing wound site[1].

Gauze: Gauze dressings are fabricated from thin layer of polymeric material that impart biocompatible, biodegradable, nontoxic, gas permeable, elastic, and transparent. Gauze dressings have an open and free weave structure that dry the wound debris and remove the necrotic tissue. Yet the phagocytic function is impaired due to tissue cooling and wound healing can be delayed due to possible hypoxia, vasoconstriction or reinjury[2].

Foam: Foam dressings have the capability to handle large amount of exudate and a favorable to be used in a chronic wound. They are required to be kept in place via another dressing since they do not adhere to the wound bed. They can be modified to be adherent

to the surrounding healthy skin tissue without causing any injury to the wound[4].

Hydrocolloid: Hydrocolloid dressings are used for noninfected wounds where they provide moist environment together with facilitating the bodies enzymes to form the granulation tissue. However, they cannot be used in the wounds around the cavities, and they may overpromote the formation of granulation tissue that causes fluid like exudate affecting the wound healing[5].

Hydrogel: Hydrogel dressings are made up of three-dimensional network of hydrophilic polymer that provides moist environment and promote wound healing by granulation tissue formation and re-epithelialization. They can be modified according to the requirement of the wound site by imparting cells, growth factors, biomolecule, antifungal, antibacterial and antiviral agents. These dressings enhance wound healing by wound contraction and can be custom made according to wound location, severity, size, and depth. They can also be applied to the irregular wounds since they cause in situ and biocompatible chemical crosslinking[2,5]**(2,5).**

METHODS

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines**.** We sought to identify suitable studies by searching the following online databases: HEC Digital Library, Wiley Online Library, Wolter Kluwer, Elsevier, and Google Scholar.The inclusion and exclusion criteria is shown in table 1.

Table 1 Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Type of study	RCTs, quasi RCTs, CCTs	Review, case study, mechanism study, research and development, preparation and storage of materials, animal experiment, marketing strategy, editorials, news, and registered clinical trials with unfinished/unreported results.
Participants	Patients with skin wounds provoked by various causes (e.g., burns, surgery, body surface ulcers, etc.).	Patients with deep burns (degrees III and IV), treatment for bone wounds, pre-operation preparation, patients using biological tissue synthesis substitutes, and patients with autologous skin cultured transplants.
Intervention	Various types of hydrogel dressings (polymeric hydrophilic compounds such as guar gum and Langmingkang® (Wound Caring)).	The hydrogel is used as a non-wound dressing such as an in vivo drug release carrier, contact lens, tissue filling material, medical sensor, etc.
Control	Any other dressing, treatment, placebo, or blank control.	Comparison of functions before and after using hydrogel dressings or comparison between different hydrogels.
Outcomes	Effective indicators including wound healing time, wound healing rate, pain scores, pain level, etc. Safety indicators referring to the incidence rate of adverse reactions including skin allergy, skin dryness, light skin, pruritus, and fever.	Long-term follow-up results such as quality of life.

*The commercial name of a hydrogel dressing.

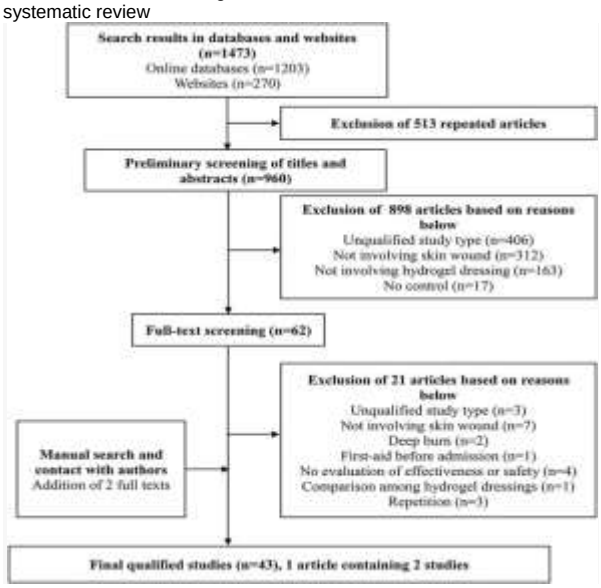
A combination of subject words and free words, the search terms included two categories: (1) “hydrogel,” “polymeric hydrophilic compound,” “guar gum,” “guar bean,” and “polyvinylpyrrolidone (PVP);” (2) “wound,” “wound surface,” and “burn.” The logical relationship was created with “OR” and “AND,” and the search formula was thereafter developed according to the characteristics of the different databases. The search strategy was improved through a pre-retrieval process. Meanwhile, unpublished studies and conference materials were manually searched, and references of the included literature were also tracked

Two reviewers carried out the preliminary screening by independently reading titles and abstracts to exclude literature that obviously did not conform with the inclusion criteria. As a further screening they read the full texts of the literature that might meet the inclusion criteria. When the two researchers' opinions differed, they consulted and discussed with a third researcher to reach a final decision. During the full-text screening, the information below would be extracted: authors, date of publication, study type, subject characteristics, sample number, loss to or withdrawal from follow-up, intervention measures, and measuring indicators, etc. In case of multiple studies in a single published work, data based on study contents would be extracted as needed. With regard to repeatedly reported studies, only the latest or the most comprehensive one was included.

RESULTS

One thousand four hundred and seventy three studies were selected by the preliminary screening. Only 43 studies were kept after screening titles, abstracts, and full-texts including 29 randomized controlled trials (RCTs) and 14 clinical controlled trials (CCTs) with a total of 3,521 patients. The Results are shown in table 2.

Table 2 PRISMA flow diagram for inclusion or exclusion of studies used for systematic review



DISCUSSION

Hydrogels have dynamic potential to be used for chronic wounds. They can be tuned to have multifunctional properties most important of which include biocompatibility, biodegradability, self-adherence, antimicrobial, angiogenic and anti-inflammatory[5]. Biocompatibility is mandatory to keep homeostasis at wound site without damaging the natural process of chronic wound healing. The degradation rate of the hydrogels is another imperative aspect since the applied hydrogel acts as a template for proliferating fibroblasts, re-epithelialization, angiogenesis, and remodeling[6]. Self-adherence of hydrogel dressing is of vital requirement to maintain its long-term stability while absorbing the exudate, providing moisture, and maintaining homeostasis around the wound site. Since the chronic wounds are susceptible to infection hence antimicrobial properties of hydrogel can prevent any possible wound infection[7]. Anti-inflammatory property of hydrogel can promote easier and faster transition from various stages of wound healing. Pro angiogenic properties can enhance the supply of oxygen, nutrients which can be very helpful for chronic wounds. Various drugs and therapeutic biomolecules can be incorporated in the functional hydrogels that provide sustained transfer of agents to the wound site for required amount of time[6]. In the next section different types of functional hydrogel dressings are discussed with examples.

Biodegradability of Hydrogels: The capacity to decay after contact with biological atmosphere is called “Biodegrability”. For chronic wounds, particularly deeper wounds[8], the biodegradation rate of hydrogel becomes an important parameter to look at as, if possible, it should complement the rate of wound healing i.e., new tissue formation and remodeling. This rate can be controlled via many approaches such as varying the crosslinking degree among polymer chains, merging variety of polymers at diverse ratios, or addition of “protease sensitive chemical functional groups”[9-14].

Usually, biodegradable hydrogels are based on collagen and gelatin[15], as they promise cell attachment and precise enzymatic biodegradation, essential for wound healing (cell proliferation and tissue restoration). By mere physical crosslinking due to temperature variation, collagen and gelatin can produce hydrogels. Yet, in order to stabilize the rapid degradation of gelatin-derived hydrogels at physiological temperatures, amount of gelatin and the amount of crosslinking can be enhanced, for e.g., cytocompatible chemical crosslinking via methacrylate groups (GelMA) is usually employed to form "photocrosslinkable hydrogels"[16,17].

Chitosan, alginate, dextran, and hyaluronic acid (Polysaccharide-based natural biodegradable hydrogels) are also commonly employed[13]. Although, wound healing stages such as, granulation, migration, and neoangiogenesis can be boosted with these Polysaccharide-based natural biodegradable hydrogels, decreased biodegradation rate is observed in comparison to ECM-derived protein-based polymers[18].

Therefore, in order to have the best of both worlds, attempts have been made to chemically crosslink proteins and polysaccharides, with adequate degradation behavior[19,20]. Carvalho and Mansur, lowered the degradation of chitosan by optimizing the photo crosslinking and gelatin content, when mixing methacrylate chitosan (ChMA) and gelatin (Gel)[10]. Photo crosslinking (stronger covalent bonds) of GelMA and hyaluronic acid have also been employed to form a hybrid hydrogel with enhanced collagenase biodegradation in comparison to pristine GelMA hydrogels[21].

By reviewing the recent literature, about biodegradability behavior of hydrogels it is evident that a lot of research is available where different materials have been crosslinked to optimize the wound healing capacity of hydrogels as well as their rate of **biodegradability. Bioadhesiveness of Hydrogels:** Flexibility and stretchability of a hydrogel makes it bioadhesive to a moist wound, thereby improving its stability, biocompatibility and patient comfort, as removal from the wound is quite smooth. Studies are available in the literature where chemical alteration with "polyphenol derived moieties", i.e., catechol, dopamine, gallic acid, or tannic acid have proven to tailor the required Bioadhesiveness of hydrogels in accordance with wound type[2,22-25]. Increased adhesion is preferred for small, shallow wounds whereas decreased adhesion is preferred for deep, large wounds which are chronic in nature[24]. In a study by Sun et al., gallic acid (GA) modification to chitosan (CS-GA) with various amounts of grafting proved to enhance bioadhesion with increasing amount of grafted GA[24]. The resulting hydrogel CS-GA was not only extremely biocompatible, adhesive, and stretchable but also permitted antioxidant and antibacterial activity. Such hydrogels showed better and efficient wound closure in comparison to pristine CS and other alternative dressings. **Antimicrobial Hydrogels for Chronic Wound Healing:** To combat high chance of infection, antimicrobial Hydrogel dressings, having antibacterial, antiviral, or antifungal components are available[26]. Addition of antibacterial agents (organic) or inorganic materials produce the Antibacterial hydrogels[21.27]. Organic materials, such as "gentamicin (GEN), vancomycin (VAN), ciprofloxacin (CIP), hematoporphyrin, fluoroquinolone, penicillin, cephalosporin, and moxifloxacin", are the most preferred antibacterial agents[28,29,30], where they inhibit bacterial DNA duplication. Drug resistance can be avoided by by altering the stiffness and degradation behavior of hydrogel which affects the release pattern of antibacterial agents in a measured and constant manner. It has also been observed that antibiotic release can also be tailored via chemical modification groups responding to environmental stimuli (pH or temperature) can tailor the[31,32]. Inorganic materials; silver (Ag) and gold (Au) ions or their nanoparticles (NPs) damage the bacterial cellular membranes or intracellular organization[21.27] and therefore ensure better antibacterial activity in comparison to organic materials. Direct loading or stabilization into micro vesicles of these inorganic noble metals with fine tuning of their physical characteristics and surface functionalization ensures antimicrobial activity. Ag+ and Ag NPs are usually preferred for their activity against both Gram-positive and Gram-negative bacteria, with no cytotoxicity in mammalian cells which needs to be sometimes addressed for some inorganic materials[33]. Metal oxides; zinc oxide (ZnO), titanium dioxide (TiO2), and copper oxide (CuO2), also demonstrated antibacterial activity when added into hydrogels[34,35].

Intrinsic antibacterial potential is also observed in Chitosan (Ch), where inhibition of bacterial DNA replication is observed because of altered bacterial cell membrane permeability[36]. Antibacterial hydrogels via functionalization with antibacterial peptides or amphoteric compounds also cause harm to the bacterial cell membrane[37,38].

Inherent antiviral hydrogels are available in the form of alginate-based biomaterials[33]. Although the mechanism of action is quite uncertain however characterization images have showed induced viral aggregation. Antiviral drugs; entecavir, penciclovir, and ganciclovir have been loaded into hydrogels with improved antiviral behavior when they are used with surfactants, polar lipids, or NPs[31,39], which even show antiviral behavior in their original state (20,30,32). Inherent antiviral behavior was observed in a study by Hu et al. (2019) where inherent antiviral hydrogels because of hydrogen bonded quadruplex structures were formed from clinically available drugs having guanine analogues[40]. **Antifungal hydrogels:** These are obtained by loading antifungal drugs (amphotericin B-AmpB) in the polymer chains and high efficacy against C. albicans strain[41]. Nevertheless, toxicity to mammalian cells and antimicrobial resistance needs to be considered with increased concentration of antifungal drugs. In this regard, immobilization of biocompatible antifungal peptides into hydrogels, making them inherent antifungal hydrogels, has been explored to decrease chances of antimicrobial resistance[30,42]. In a study by Liu et al. 2019 long-lasting free radicals in plasma-activated water were utilized to prepare polyacrylamide hydrogels, where the plasma treatment time dictated the strength of antifungal activity[43].

Anti-inflammatory Hydrogels for chronic wound healing: Continued inflammation may lead to abundant amount of reactive oxygen species in the wounded area. Anti-inflammatory hydrogels increase the accumulation of macrophages in wound area and reduce ROS. This process allows the changeover from the inflammatory phase to the proliferation. The healing enhances and reduces its total duration[1]. The hydrogels may also have intrinsic anti-inflammatory qualities. Chitosan and its products can control the inflammation process by boosting the secretion of TGF-b, PDGF, and IL-1[2,3]. Hyaluronic acid also shows inherent anti-inflammatory properties which is also a main constituent of the skin ECM[4,5]. Phenol compounds may be chemically attached to hydrogels giving anti-inflammatory properties[1]. Stimulating the body's innate immune system by altering the hydrogels with targeting agents can also be used to develop anti-inflammatory properties. For example, aiming the sphingosine-1-phosphate receptor can activate inflammatory cells[6]. Bioceramics containing hydrogels may also exhibit anti-inflammatory activity during wound healing process[7]. Inflammation reduced by using bioceramic particles encapsulated in gelatin/PCL nanofibers with controlled release of silicon (Si) ions[8,9].

As continued inflammation leads to excessive build-up of ROS surrounding chronic wounds, the antioxidant ability of cells to scavenge ROS becomes limited. A few anti-inflammatory hydrogels also display antioxidative function. An example is catechol-modified hydrogels which show both anti-inflammatory and antioxidant activity[10,11].

Pro-Angiogenic Hydrogels for Chronic Wound Healing: Inadequate nutrient and oxygen supply to the wound region is one of the likely reasons for delayed chronic wound healing. Angiogenesis plays a critical part in wound healing for essential quantity of nutrients[1]. Some hydrogels are pro-angiogenic intrinsically. They can also be made proangiogenic by including angiogenesis stimulating factors. Patra et al. (2012) prepared A. mylitta silk fibroin (AM) hydrogel with intrinsic pro-angiogenicity[13].

Sheng et al designed a novel bioactive photothermal hydrogel with "hot spring effect" based on fayalite (FA) and N, O-carboxymethyl chitosan (NOCS), which released bioactive ions creating hot ion environment in wound area. The release of bioactive ions triggered different angiogenic factors and signaling pathways[14].

Drug or Therapeutic Agent Releasing Hydrogels for Chronic Wound Healing: Controlled and sustained release of various types of drugs and therapeutic agents incorporated into hydrogels can improve wound healing process. Hydrogel's stiffness and pore size have an impact on the released amount of physically encapsulated drug. Drugs can be combined into hydrogels using covalent bonding for controlled drug release kinetics[15].

Stimuli-responsive hybrid hydrogels respond to any change in biological and physicochemical conditions, such as pH or temperature in the wound area. They are also helpful for controlled delivery of drugs[16,17]. Higher levels of glucose cause acidic conditions in diabetic foot ulcers. A hybrid hydrogel (Gel) composed of N-carboxyethyl Chitosan (N-CS), Hyaluronic acid aldehyde (HA-ALD), and adipic acid dihydrazide (ADH) was developed. Insulin was released by increased acidity in the wound area. In response to an acidic pH, sustained insulin release resulted in decreased glucose levels and showed effective healing of a full thickness wound by promoted collagen deposition, and enhanced tissue formation[18]. In another study, a thermosensitive hybrid hydrogel was developed for the controlled release of MMP-siRNA to silence the MMP-9 gene[16].

CONCLUSION

Chronic wounds compromise the day-to-day life and prove to be a costly treatment affair due to delayed wound healing. Dressings are the first line of treatment choice for chronic wounds. They are available as films, gauze, foams, hydrocolloids, and hydrogels. Hydrogel dressings are valuable for chronic wound treatment because of their purpose-built quality according to the precise requirements of chronic wound treatment. They encourage wound healing by promoting autolytic debridement and moisture in wound bed so that granulation and re-epithelialization occurs. They have additional benefit of biodegradability and if removal is required, ease of removal from chronic wounds with no damage to the healing wound tissue. The various characteristics of Hydrogels can be precisely modified such as adhesiveness, antimicrobial nature, vascularization ability, anti-inflammatory properties, and antioxidant features. It is awaited that such multi-modified hydrogel dressings will evolve the treatment planning for chronic wounds in near future. All the above-reported results strongly indicate that hydrogel products are effective and safe in wound management. Furthermore, there is a need for high-quality and international multi-center RCTs reporting adverse reactions to help clinicians make informed decisions on the best options for patients suffering from skin wounds.

Conflict of interest: Nil

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