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The effect of Ringer's solution within a dressing to elicit pain relief

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Clinical studies suggest that dressings containing Ringer's solution, such as the TenderWet and HydroClean families, provide relief from wound pain. This report reviews the available evidence and possible mechanisms for the relief of wound pain by these dressings. The ability of dressings containing Ringer's solution to provide pain relief is likely to be through providing a moist environment that is favourable for wound healing; furthermore, the dressing augments the protective barrier function by having additional fluid under the dressing, which covers exposed nerve endings and protects against friction damage. Ringer's solution will have a dilution effect and an influence on the pH of exudate. Diluting cytokines within the exudate would be expected to decrease inflammation in chronic wounds and reduce the influence of caustic components such as matrix metalloproteases (MMPs). Altering the pH of the wound bed could inactivate proteins and glycoproteins implicated in the pain response such as MMPs and sodium and calcium channels. The moist environment may also be better at recruiting leukocytes that release natural painkillers at areas of injury. These mechanisms are likely to act in combination to explain why dressings containing Ringer's solution can have analgesic effects.

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pain; analgesics; Ringer's solution; occlusive dressings

The main functions of a wound dressing are to protect the wound and allow rapid healing; however, another important role is the dressing's ability to reduce wound pain. Pain is a major concern for patients with a wide range of both acute and chronic wounds.[1,2] Acute wounds, such as burns, and chronic wounds, such as pressure ulcers (PUs), are often considered to be particularly painful. Nevertheless, until recently, pain was often considered to be of secondary importance to the healing process in the minds of wound care providers.[3] For chronic wounds in particular, pain is often under-recognised and under-treated.[4] If pain is long-term it can result in a decrease in activity and loss of independence, a lack of energy and appetite, mood changes and depression.[4] It is now clear that pain relief is important for effective wound healing; as the anxiety and stress over wound pain increases, so does the likelihood of experiencing pain and this cycle is detrimental to the healing process.[5,6]

Wound-related pain may involve persistent pain that is usually associated with the underlying wound aetiology. Cyclic acute pain is induced by repeated interventions such as cleaning and dressing change, while non-cyclic acute pain results from one-off procedures such as debridement.[7] Alongside the direct pain resulting from the wound, additional factors may increase wound-related pain, including infection in the wound and cellulitis in the periwound skin.[8,9]

The stress and anxiety of wound pain is a particular concern for patients at dressing change.[10] One method of pain relief is the use of analgesic drugs, such as non-steroidal anti-inflammatory drugs. These may produce some unwanted side effects such as gastric ulcers and heart problems in patients with a history of cardiac failure or those receiving other medications;[11,12] especially if in high doses and/or long-term use is needed. The analgesic effect of wound dressings can improve the patient's quality of life (QoL), reduce the need to provide analgesic drugs and even speed healing. For these reasons, pain has become an important consideration, along with improved outcomes, in favour of using advanced wound dressings.[13]

A number of advanced dressings have been developed that assist healing and some of these have been developed with the aim of reducing wound pain. As pain at dressing change is often of most concern to patients,[10] the use of non-traumatic wound dressings reduces pain and anxiety.[14] These prevent the damage that often occurs with traditional dressings that adhere to the wound bed or periwound skin, requiring painful removal.[15] Other dressings have been designed to reduce persistent wound pain while in place. These include foam dressings containing ibuprofen, an analgesic and anti-inflammatory drug, which is released into the healing wound bed.[16,17] Their use, while likely to be beneficial to many patients, may have side effects, although this is likely

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reduced by local release at low doses.[4] However, due to the anti-inflammatory action, they have the potential to inhibit the inflammation required to progress wound healing.[18]

Previous theoretical work has suggested ten potential mechanisms for the analgesic effect of a dressing.[19] These mechanisms include aspects common to most wound dressings, such as covering the wound to remove it from sight, which decreases anxiety and acting as a barrier to mechanical stimuli. However, some mechanisms are likely to be influenced by the properties of different dressings, for example occlusive dressings maintain a moist wound environment and accumulate fluid around the wound and this has been shown to reduce wound pain.[20,21]

Dressings such as TenderWet and HydroClean (Paul Hartmann Ltd) incorporate Ringer's solution with the aim of providing an optimal wound healing environment with active wound cleansing.[22] They are designed to clean the wound and be non-traumatic, reducing the chance of pain by the dressing being in place for longer periods and not causing damage to the wound or periwound skin on removal.[22] By maintaining a regulated moist wound healing environment, it is likely that a dressing containing a carefully balanced isotonic solution such as Ringer's solution may provide analgesia for persistent wound pain. The moist barrier may have an additional cushioning effect and protect against friction,[19] dilute pain-causing factors such as prostaglandins, kinins, cytokines and matrix metalloproteases (MMPs) and reduce inflammation.[23,24,25] A pH balanced Ringer's solution would be expected to modify the pH of exudate and this will influence the action of sodium and calcium channels involved in the pain response.[26] The nature of the isotonic solution might also be expected to recruit leukocytes that release natural painkillers.[27,28]

Clinical studies suggest that Ringer's solution within a wound dressing does reduce wound pain as patients experienced decreased pain after treatment and low levels of pain at dressing change.[29–32] Here we review the available studies and present the suggested mechanisms by which these dressings may provide an analgesic effect that is beneficial to the patient and to the progression of wound healing.

Methods

To investigate the analgesic nature of dressings containing Ringer's solution a search of the literature was performed, including those listed in PubMed/Medline, to find studies that reported pain in terms of wound pain and pain at dressing change when dressings containing Ringer's solution were used. The terms 'Ringer's solution', 'dressing', 'pain' were used for the search. The search was undertaken in September 2015 and included all reports up to that time point. Reports available from the dressing manufacturer were also consulted (Paul Hartmann Ltd). In these cases the clinical data was assigned the status of 'Data on file'.[33] A review of the available literature was then performed to assess the mechanisms by which the dressings with integrated Ringer's solution might provide pain relief. We identified 10 studies, four clinical studies and six case studies.

Clinical evidence

Data is available from four clinical studies to suggest dressings with Ringer's solution provided some degree of wound pain relief.[29–32] However, it should be noted that each of these studies was observational, without comparisons between the dressings with Ringer's solution and alternative advanced dressings, so the quality of the evidence presented is low.

In a multicentre observational study, 403 patients with chronic wounds (average duration of 2 months) were treated for an average of 1 month with a dressing containing Ringer's (data on file).[30] A reduction in pain was observed; at the start of the treatment 65% reported 'mild' or 'severe' pain; this was significantly reduced at the end of treatment to 13%. The dressing was atraumatic and pain at dressing change was reported as low, with 89% of patients rating the dressing as 'good' or 'very good' with regard to pain during dressing change.

A second multicentre observational study (170 patients) also reported decreased wound pain.[31] A variety of chronic wounds that had persisted for an average of 5 months were treated with a dressing containing Ringer's for an observational period of 8 days (data on file).[31] At the start of the treatment, 35% of patients suffered 'moderate' to 'severe' wound pain, whereas at the end of the treatment this was reduced to 19%. Parallel to wound pain, the proportion of 'moderate' to 'severe' pain at dressing change decreased from 28% at the start to 11% at the end of treatment.

In a single-centre observational study, 37 patients with venous leg ulcers (VLUs) were treated with a dressing containing Ringer's for an average of 19 days. Most patients (89%) experienced low or no pain.[32] There was no record of how much pain was experienced before this treatment, so we cannot compare before and after treatment in the study. However, as pain is the biggest problem faced by patients with these wounds, and the reported levels of high pain are between 29–64% with chronic VLUs,[34] these figures are encouraging.

The final study was a prospective open-label observational study of 221 patients with a variety of chronic wounds. The wounds were treated for 1 month with a dressing containing Ringer's. Pain reported as 'intermediate' to 'high' decreased from 64% to 19% of patients.[29]

Case reports also provide additional information that suggests wound pain experienced by patients is lowered with dressings containing Ringer's. Again

these presentations give no comparison between dressings and so the quality of the evidence is, low. There are six reports available (data on file).[35–40]

In a report of two cases, the first was a 40-year-old patient with a VLU who had suffered with recurrent ulcers for four years, [36] who was treated with a dressing containing Ringer's over a 3-week period. Upon the initial examination the patient complained of very severe wound pain, which had been treated with ibuprofen and morphine. During the 3-week treatment period, the slough and wound exudate levels were reduced and wound pain decreased significantly. At the end of the treatment, the patient considered the wound pain to be 'moderate'. The second was a 45-year-old with a chronic wound after an insect bite. The wound had not healed after 45 days and the patient complained of severe wound pain. Before the application of dressing containing Ringer's, necrotic tissue was surgically debrided. Using the dressing re-epithelialisation progressed. The patient tolerated the dressing well and the wearing comfort was assessed as very good, and wound pain decreased.[36]

A case series of five patients with second- and third-degree burns compared the level of pain experienced before and after use of the dressing in four of the five patients.[35] Of the four patients three reported decreased pain while the remaining patient already had low pain levels.[35]

Other single clinical case studies have also noted some level of pain relief, using a variety of different dressings containing Ringer's.[37–40] A 74-year-old patient with a VLU complicated by pyoderma gangrenosum noted pain relief upon application;[40] a 82-year old who had significant skin tear due to trauma experienced pain relief upon application providing a moist wound environment.[39]

A 72-year-old patient had developed a sacral PU due to complete immobility. The PU was partially covered by black/yellow necrotic tissue and was very painful. The dressing containing Ringer's promoted autolytic debridement, with eventual reduction in exudate production levels and reduction in wound margin inflammation. The patient reported accompanying pain relief with improvement of the wound bed.[37] Finally, in a 69-year-old patient who had suffered a wound to the tibia region of leg and developed tissue necrosis and periwound inflammation, it was found that because of the minimal number of dressing changes and the atraumatic nature, that dressing changes were accompanied by little or no pain.[38]

Limitations

In summary, there is low-quality evidence that dressings containing Ringer's solution reduce wound pain. However, there are no detailed comparisons with other dressings, so we cannot conclude that these dressings are superior to others. As a wound heals, the pain would be expected to decrease, so more evidence is needed in terms of the pain relief provided by the dressings rather than it being the normal result of rapid wound healing. High-quality research is required; in particular, randomised controlled trials would provide the highest level of evidence for the use of these dressings.

Mechanisms for the analgesic effect

The effect of Ringer's solution can be studied by examining ten potential mechanisms for the analgesic effect of wound dressings,[19] and adapting them based on the physical properties of the solution. The mechanisms that are likely to be the most influential are those that involve the moist environment encouraged by the Ringer's solution. It is well established that a moist wound environment promotes acute wound healing by increasing re-epithelialisation and reducing scar tissue formation. This process probably involves encouraging cell proliferation and supporting conditions favourable for growth factors.[41] With this in mind, there are four main mechanisms worth consideration.

Mechanism 1: protective barrier

The barrier formed by a dressing is critical to its function of protecting the wound from further mechanical injury or infection;[42] this barrier also provides a cover to exposed nerve endings.[19] By augmenting the natural fluid created under the dressing the effect of the Ringer's solution is to create an additional barrier similar to a cushion effect we speculate. An analgesic effect may be elicited by this extra barrier in a similar way to other occlusive dressings that maintain a moist environment.[43] Increasing the barrier formed by the dressing would also be expected to reduce friction. Friction is a major cause of damage to periwound skin and the edges of wounds; supplementing the moist environment with a solution with a balanced pH could protect the wound against the pain and damage caused by friction and produce analgesia as a result.

Mechanism 2: dilution of exudate

The damage to the skin can also be increased by caustic wound exudate.[44] Cytokines are a large, diverse group of small proteins that are secreted from cells involved in the immune and inflammatory responses, such as macrophages, and have a wide range of different roles in cell signalling.[45] They are vital for the process of wound healing, which involves a balance between pro- and anti-inflammatory cytokines released from cells that are in and around the wound bed and cells recruited to the wound bed.[46] This robust inflammatory response, while required for wound healing, can also have detrimental effects in terms of the pain experienced by the patient. Cytokines are implicated in causing pain,[27,28,47] and pro-inflammatory

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cytokines, by increasing inflammation, will induce pain.[20,23,43] The presence of Ringer's solution is likely to dilute the cytokines within the wound exudate, which may cause a decrease in inflammation in the types of wounds where excessive inflammation may be detrimental, such as in chronic wounds.[47] In addition, dilution could reduce the influence of the caustic molecules such as MMPs. Similar to cytokines, MMPs have a vital role in acute wound healing; in this case, they are involved in the breakdown of the extracellular matrix proteins such as collagen and elastin;[48] however, MMPs are known to cause pain,[49] and in chronic wounds they can be overexpressed, resulting in damage to periwound skin and increased inflammation.[50] Therefore, by considering these roles of cytokines and MMPs in inflammation it may be concluded that their dilution could reduce pain.

Mechanism 3: balancing the exudate pH and ionic composition

Ringer's solution is isotonic and by diluting the wound exudate it may influence the pH and maintain the ionic composition of the wound bed. In the original description Sydney Ringer examined beating frog hearts.[51] His newly reported solution kept the heart beating much longer compared with simple saline solution. From his description the ionic composition of the Ringer's solution supported cellular depolarisation and repolarisation processes in the heart muscle.[51] Depolarisation and repolarisation also underlie pain perception originating from free nerve endings.

Modifying the pH will also affect the function of sodium and calcium channels in the nerve endings, ion channels known to play a role in pain.[52–56] Also, changes in acidity are known to denature proteins, and as ion channels are glycoproteins there is a chance that even if they are not fully denatured they may be structurally altered by a modified pH affecting their function. In addition to depolarisation and repolarisation processes, cell functions are maintained for longer periods when cells are exposed to Ringer's solution compared with normal saline fluid.[57,58] By modulating the extracellular ion composition and pH together, Ringer's solution could contribute to pain reduction by stabilising nerve endings and supporting their cellular synthetic functions.

Furthermore, sodium bicarbonate-containing solutions may also have a direct pain-reducing effect, and have been included in combination with other drugs to reduce pain in many different conditions such as cancer, sore throats and carpal tunnel syndrome;[59–61] for example, a study investigating methods of reducing the intense discomfort experienced during administration of intravenous rocuronium, an anaesthetic agent, found when 8.4% sodium bicarbonate was added to the agent, pain was markedly reduced.[62]

Mechanism 4: recruiting leukocytes

The isotonic nature of Ringer's solution may recruit natural painkillers. It is well known that leukocytes (a type of white blood cell) are rapidly recruited to wounds as part of the immune and inflammatory responses, by proteins and chemokines released at the site of injury.[63] However, leukocytes have an additional role in pain relief. Leukocytes contain natural opioids and when reaching a wound bed they migrate to the inflamed areas and release the opioids to produce analgesia.[28,64,65] This is a natural process that occurs in response to injury, but it can be expected to be enhanced by the favourable moist conditions provided by the dressing, because migration of leukocytes requires provision of functional adhesion molecules such as integrins, which need a moist environment for their correct structural integrity and action as attraction molecules.[66]

Summary

It is likely that a combination of all four mechanisms will contribute to the analgesia experienced by patients treated with Ringer's solution within a dressing, rather than any one individual effect. In fact in many respects these mechanisms overlap as they all rely on the provision of a controlled moist environment. The importance of each mechanism is likely to be dependent upon the type of wound. For example, in acute wounds the initial protective function and provision of an environment that is favourable for rapid wound healing are likely to be most important while in chronic wounds controlling the detrimental cascade of the inflammatory response is likely to be most important, not just for relief of wound pain, but also for developing conditions that are favourable for eventual wound healing.

Conclusion

Wound dressings provide pain relief by a variety of different mechanisms. A controlled moist environment that is favourable for rapid healing would be expected to provide a high degree of pain relief and is the basis of many advanced dressings available today. Dressings containing Ringer's solution would be expected to offer additional protection to the nerve endings in the wound, decrease friction, dilute the detrimental effects of wound exudate and encourage the recruitment of leukocytes that provide endogenous pain relief. The reported level of wound pain in patients treated with dressings containing Ringer's solution in clinical studies was low and this data needs to be supported by more studies and comparisons with other dressings. Controlled randomised trials are needed to reveal the true value of these dressings for pain relief. ■

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