Clinical assessment of the pharmaceutical properties of non-drug loaded hydrogel semi-solids in lacerations

Carol Little, Julie McDonald, Oonagh Kelly, Mark Jenkins, Diarmaid Murphy, Paul McCarron

Abstract

Background: The aim of this project was to assess the potential role of an innovative, cross-linked, semi-solid dosage form as a means of topical drug delivery to acute lacerations. *Aim:* The objectives of the project were to formulate and evaluate a number of semi-solid dosage forms clinically, which have a range of viscosities and have been specifically designed to allow them to reside in, achieve intimate contact with, and be removed cleanly from a laceration that requires suturing. *Methods:* This trial was conducted in a busy urban Emergency Medicine (EM) department. All adult patients that presented to the EM department with a laceration were invited to enrol in the study. The study population consisted of 25 adults, older than 18 years, who had a laceration which required anaesthesia before repair. *Results:* In this pilot study of formulation suitability, formulation III was shown to have the most appropriate physical characteristics for use in the treatment of lacerations. *Conclusion:* It has been shown that an innovative, cross-linked, semi-solid dosage form has the properties to be used for the potential topical delivery of drug substances into lacerations. *Conflict of interest:* None.

KEY WORDS

Laceration
Non drug-loaded hydrogel semi-solids
Laceration repair

One of the principal concerns during any laceration repair is to ensure effective anaesthesia at the site of trauma, so making the cleaning and repair as painless a process as possible for the patient. This is generally achieved by using a local anaesthetic agent injected proximal to the site. This can be a painful procedure and can also distort the tissue planes, resulting in inexact laceration repair (Lener et al, 1997; Zempsky and Karasic, 1997; Hollander and Singer, 1999; Schecter et al, 2005). It is envisaged that topical anaesthesia has the potential to alleviate or eliminate many of the disadvantages associated with infiltrative anaesthesia without compromising on good surgical toilet, effective analgesia or excellent wound repair (Chad et al, 2007). Bush (2000) believes that an overall lack of experience, ineffectiveness and issues relating to availability are some of the reasons why topical anaesthesia is not widely implemented in the UK.

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Conventional, semi-solid pharmaceutical preparations, such as creams and gels, possess an array of rheological properties, ranging from simple Newtonian flow, i.e. a linear relationship between rate of shear and shear stress, e.g. water, through to more complex profiles, such as plastic, pseudoplastic and dilatant flows. Plastic flow arises where shear only occurs after a certain yield stress has been exceeded but then becomes linear; pseudoplastic flow arises where the material becomes more fluid as it is spread; dilatant flow displays the opposite effect, becoming more difficult to spread the more it is worked. The majority of currently used semi-solids, however, are not of sufficient cohesive structure to remain intact on removal. Therefore, this trial was undertaken to determine if an innovative, cross-linked, poly (vinyl alcohol), semi-solid dosage form has the required rheology and flow properties to allow it to reside in, and be removed cleanly from a deep laceration. A blank hydrogel containing no active drug was evaluated in adults to assess its performance during and following application. A hydrogel system such as this has not been described in the literature for use in lacerations.

Aim

The aim of this project was to evaluate clinically an innovative, cross-linked,

Carol Little is Emergency Medicine Sister; Julie McDonald is Emergency Medicine Staff Nurse; Oonagh Kelly is Emergency Medicine Staff Nurse; Mark Jenkins is Emergency Medicine Consultant, all at the Department of Emergency Medicine, Antrim Area Hospital, Antrim; Diarmaid Murphy is Research Fellow, School of Pharmacy, Queen's University Belfast, Medical Biology Centre, Belfast; Paul McCarron is Chair in Pharmaceutical Sciences Department of Pharmacy and Pharmaceutical Sciences, University of Ulster, Londonderry

semi-solid dosage form, as described in the work of Loughlin et al (2008), and to ascertain whether such a hydrogel material could be used in future for the topical drug delivery of anaesthetic drug substances into lacerations before suturing. This study aims also to select the optimal physical properties of a range of candidate hydrogels once administered to the wound site, and to access how performance is affected by the presence of exudate and blood contamination.

Methods

All adult patients (18+) that presented to the Emergency Medicine (EM) department with a laceration, and who met the study entry criteria (*Table 1*) were invited to enrol in the study. Informed consent was obtained in all cases. This study was approved by a Health Service Research Ethics Committee. All study procedures were conducted according to the protocol submitted to the ethics committee.

Formulated hydrogels were numbered I – VI, labelled according to physical characteristics, with formulation I being the stiffest hydrogel. The formulation development and physical characterisation of the hydrogels have been described elsewhere (Loughlin et al, 2008). In this study, blank formulations containing no active drug were evaluated in adults to ensure that the optimum formulation was taken forward in future developments.

Study protocol

The research nurse approached patients attending the emergency department with lacerations that met pre-defined inclusion and exclusion criteria (*Table 1*). The study population consisted of 25 adults who gave their written, informed consent after considering the information provided. Thereafter, the wound site was infiltrated with lidocaine and photographed. The selected hydrogel formulation was applied and left for five minutes to allow it to flow into the wound cavity sufficiently and reside there. The wound was photographed with the hydrogel in situ, both at the start and the end of the five-minute period. After this period, the hydrogel was removed and the wound was photographed again. Following hydrogel removal, the wound was treated conservatively with further

cleaning and suturing as per hospital policy before being photographed at the end of treatment. Details of the participants were also recorded, capturing age, sex, site of wound, size of wound and number of sutures. Clinical staff in the EM department completed a form detailing any problems found in the application or use of the hydrogel.

Measurements

An in-house evaluation tool, comprising eight characteristics, was used to describe the clinical performance of the hydrogels. A rating scale ranging from 1–5, with one representing strongly agree and five representing strongly disagree, was used to evaluate the formulations.

These characteristics were:

- Ease of removal from container
- Application of sufficient quantity to cover wound
- Contents did not spill from wound site
- Flow into wound cavity
- Resided in cavity without manipulation
- Ease of removal from wound
- Removal in one piece
- Sensation on removal of hydrogel.

Each formulation obtained an overall score ranging from 8–40. The best possible score being 8 (i.e. a score of 1 for each characteristic) and 40 representing the worst possible score (a score of 8 for each characteristic). In addition, a free response section was included to allow the clinician to record any other issues noted in the application or use of the gel.

Results

In total, 29 participants were enrolled in the study with an age range of 18–80 years. Six different formulations were tested, most done in quintuplicate. The majority of the participants were male (17/25), and the most common site of hydrogel application was the upper extremities (12/29). Laceration length varied from 1.0–8.0cm. The scoring mechanism applied during clinical use gave a lower score to those formulations that exhibited better physical properties. A summary of the clinical evaluation score of each hydrogel is provided in *Table 2*.

The first parameter assessed in the trial was the ease of removal from the container. Formulations III and IV scored equally well on their ease of removal, being easier to manipulate than the other formulations and less likely to stick to the side of the container or the healthcare professional's gloves. As a result of their low viscosity, formulations V and VI were sticky, making them difficult to remove from both container and gloves. It was also difficult to acquire the ideal amount of hydrogel to place over the wound. On the other hand, formulation I was rigid and its removal from the container proved difficult.

The second parameter assessed if the hydrogel could be applied in sufficient quantity to cover the wound. Formulations II and III scored equally well, as these proved straightforward to manipulate and get the right quantity to apply. An example of the application of formulation III is shown in *Figure 1*, illustrating how this hydrogel has flowed into a scalp laceration in such a way as to encompass the entire wound. Related closely to this was an assessment of spillage from the wound site (parameter 3). Formulation III was found to be the best at occupying the entire wound site and resisting excess overflow. Although formulation I was resistant to overflow, it was too rigid to allow effective flow into the wound cavity.

The information gathered in parameters 5 and 6 concerned the hydrogels' abilities to fill the wound and remain without manipulation. When formulation III was placed on the wound, it remained static for five minutes without manipulation, as shown in *Figure 1*. *Figure 2* shows the negative relief of the wound featured in *Figure 1*. Formulations V and VI scored poorly on these parameters. Their viscosity was such that they did not reside in the wound cavity for a useful period of time. As formulations I and II were rigid,

Table 1

Study inclusion and exclusion criteria

Inclusion criteria
>18 years old; able to provide informed written consent; have a laceration <8cms that requires analgesia before repair
Exclusion criteria
Wounds that could be approximated by tissue adhesives/steristrips; animal/human bites; gross contamination; puncture/crush wounds; wounds crossing joints; laceration to tendon/nerve/cartilage; areas supplied by terminal arteries; collagen vascular disease; immunodeficiency; diabetes; bleeding disorders; warfarin therapy; lidocaine allergy; scalp lacerations and patients receiving medication that predisposes them to methaemoglobinaemia

Table 2

Scores of the six formulations using the clinical evaluation tool

Formulation	Number of gel usage	Mean score (out of 40)	Range
1	5	18.4	14/40–25/40
2	5	10.8	10/40–12/40
3	5	9.0	8/40–11/40
4	5	16.2	12/40–19/40
5	5	28.6	11/40–39/40
6	4	25.3	20/40–36/40

they resided on top of the wound for five minutes without manipulation, but it was clear from inspection of the removed hydrogels that they had not filled the wound cavities effectively.

Parameters 6 and 7 focused on the performance of the hydrogels during the removal process. Formulation VI performed poorly during these tests, whereas formulation III was particularly good, as shown in *Figure 3*. The outline of the wound cavity is identifiable on this photograph. Formulation 6 adhered to the wound margins and debris remained in the wound cavity. Similarly, the use of formulations IV, V and VI also resulted in hydrogel remnants following removal. On each occasion of testing, it was possible to remove formulation III intact, as shown in *Figure 3*.

The final aspect of testing was to measure sensation upon hydrogel removal. On each occasion of testing, the participant had their wound infiltrated with lidocaine before the hydrogel was applied. Therefore, experience of pain upon removal was unlikely. In some cases, i.e. when formulations I and V were applied, further lidocaine was required as the patient stated that they felt pain on removal of the hydrogel. When the results from the overall assessment as shown in *Table 1* are considered, it is clear that formulation III was superior, with an average score of 9.0/40. Formulation V was shown to be the poorest performer, with an overall mean score of 28.6/40.

Follow-up

Of the 29 participants enrolled in the study, 68% (n=17) returned to the EM department for removal of sutures (ROS). Of the remaining eight participants, one was transferred to another hospital, three attended their local treatment room for ROS and one participant had their sutures removed by a family nurse.

Discussion

The use of topical anaesthesia in emergency medicine has been reported for several years now in both the USA and Australia (Young et al, 2005). It is obvious that using this approach has the potential to reduce or eliminate many of the disadvantages associated with infiltrative anaesthesia, such as pain,

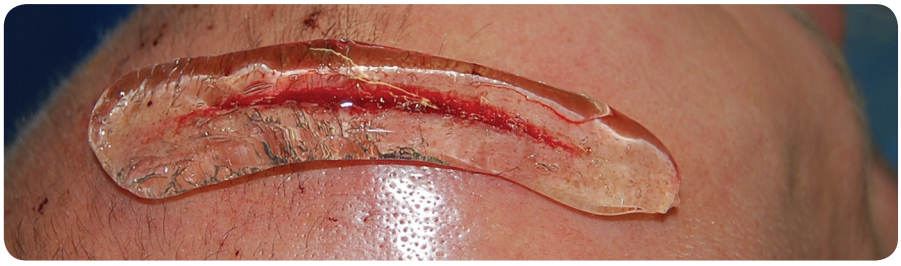

Figure 1. Application of formulation III to a scalp laceration.

Figure 2. Negative relief of the wound featured in *Figure 1*.

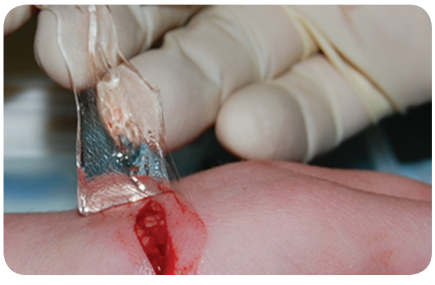

Figure 3. Formulation III removed from a wound fully intact with visible outline of wound cavity.

distortion of tissue plains and patients with needle phobias. Furthermore, using topical preparations is preferred by patients, especially those with a degree of needle phobia, and the approach has been shown to improve patient satisfaction and increase co-operation (Van-Liaw, 2001). However, topical anaesthetic formulations themselves are not without their disadvantages (Bush, 2000), such as messiness during application and removal, and an inability to achieve an adequate depth of penetration into the wound cavity. Inevitably, such drawbacks have contributed to a general decline of use in many EM departments (Bjerring and Arendt-Nielsen, 1990; de Waard-van der Spek et al, 1992).

The aim of this study was to evaluate the performance of a novel hydrogel material in acute lacerations in the clinic. As described in the work of Loughlin et al (2008), novel poly (vinyl alcohol) based topical formulations display particular physical characteristics that may be of use in the development of topical drug delivery systems for acute lacerations. In this context, it would be pointless to develop a hydrogel that was not workable either because it was too rigid or too fluid. This pilot study has shown that while a hard hydrogel, such as formulations I and II will remain intact on a wound surface, they will not flow sufficiently into a wound. On the other hand, a formulation of excessively low viscosity, such as formulations IV, V or VI, will flow out of a wound and not reside sufficiently long enough to bring about effective drug delivery. There is also an associated risk with these formulations as they were difficult to remove from the wound, although with thorough irrigation, all traces of hydrogel were removed. From the results outlined above, it is clear that formulation III is optimal.

Although this pilot study was testing the physical properties of a non-drug-loaded variant of the hydrogel, the results obtained provide a set of benchmark specifications that the drug-loaded versions must match. It may prove necessary to balance the need for rapid drug delivery into the tissues with the formulation requirements regarding ease of removal. However, as previous work has demonstrated reasonable release over time-scales practical in an EM department, the authors anticipate that this should prove achievable (Loughlin et al, 2008). Like any medicinal product, it is desirable for a topical anaesthetic to be user-friendly. It would be ideal to produce a drug-loaded hydrogel which could address each of the parameters outlined in this study and overcome some, if not all, of the disadvantages documented in the literature today, in relation to the problems associated with topical anaesthetic formulations. In the future, this project aims to build on the previous work and test a formulation with the appropriate physical and drug release characteristics in wounds in both children and adults.

Recommendations for practice

The experience gained from evaluating these blank hydrogels within the wound site will be invaluable in the subsequent development of a drug-loaded hydrogel.

Conclusion

In this pilot study of formulation suitability, formulation III was shown to have the most appropriate physical characteristics for use in the treatment of lacerations. No formulation-attributable adverse reactions

Key points

- The goal of laceration management is to ensure effective anaesthesia making cleaning and repair as painless as possible.
- Topical anaesthesia has the potential to provide effective anaesthesia, enabling good surgical toilet and good wound repair without tissue distortion.
- A hydrogel system such as this has not been described in literature elsewhere as being used in the treatment and repair of lacerations.
- This pilot study tested the physical characteristics of a non-drug loaded hydrogel; the results obtained provide benchmark specifications that the drug-loaded versions must match.

were noted in any of the participants. Further formulation development is currently underway and the clinical evaluation of drug-loaded formulations matching these physical characteristics (i.e. gel hardness, flow and adhesiveness) is planned. These findings may be important as successful development of a drug-loaded formulation requires the delivery system to display the appropriate physical characteristics. **WUK**

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