Negative pressure wound therapy versus standard treatment in patients with acute conflict-related extremity wounds: a pragmatic, multisite, randomised controlled trial

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Summary

Background In armed conflict, injuries among civilians are usually complex and commonly affect the extremities. Negative pressure wound therapy (NPWT) is an alternative to standard treatment of acute conflict-related extremity wounds. We aimed to compare the safety and effectiveness of NPWT with that of standard treatment.

Methods In this pragmatic, randomised, controlled superiority trial done at two civilian hospitals in Jordan and Iraq, we recruited patients aged 18 years or older, presenting with a conflict-related extremity wound within 72 h after injury. Participants were assigned (1:1) to receive either NPWT or standard treatment. We used a predefined, computer-generated randomisation list with three block sizes. Participants and their treating physicians were not masked to treatment allocation. The primary endpoint was wound closure by day 5. The coprimary endpoint was net clinical benefit, defined as a composite of wound closure by day 5 and freedom from any bleeding, wound infection, sepsis, or amputation of the index limb. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT02444598, and is closed to accrual.

Findings Between June 9, 2015, and Oct 24, 2018, 174 patients were randomly assigned to either the NPWT group (n=88) or the standard treatment group (n=86). Five patients in the NPWT group and four in the standard treatment group were excluded from the intention-to-treat analysis. By day 5, 41 (49%) of 83 participants in the NPWT group and 49 (60%) of 82 participants in the standard treatment group had closed wounds, with an absolute difference of 10 percentage points (95% CI –5 to 25, p=0·212; risk ratio [RR] 0·83, 95% CI 0·62 to 1·09). Net clinical benefit was seen in 33 (41%) of 81 participants in the NPWT group and 34 (44%) of 78 participants in the standard treatment group, with an absolute difference of 3 percentage points (95% CI –12 to 18, p=0·750; RR 0·93, 95% CI 0·65 to 1·35). There was one in-hospital death in the standard treatment group and none in the NPWT group. The proportion of participants with sepsis, bleeding leading to blood transfusion, and limb amputation did not differ between groups.

Interpretation NPWT did not yield superior clinical outcomes compared with standard treatment for acute conflict-related extremity wounds. The results of this study not only question the use of NPWT, but also question the tendency for new and costly treatments to be introduced into resource-limited conflict settings without supporting evidence for their effectiveness. This study shows that high-quality, randomised trials in challenging settings are possible, and our findings support the call for further research that will generate context-specific evidence.

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See **Comment** page e319

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Introduction

In 2017, armed conflict killed about 95 000 people worldwide, nearly half of them in Iraq and Syria.[1] In these countries, conflict-related injuries are the leading cause of loss of disability-adjusted life-years.[2] A report[3] from the Syrian armed conflict found that 70% of direct deaths were civilians. Conflict-related injuries in civilians predominantly affect the extremities, and comprise wounds with or without fractures.[4] Clinical management of conflict-related extremity wounds is challenging, requiring substantial resources, and it is often complicated by infection.[5–7] Wound complications can result in prolonged treatment times and increased risk of morbidity and mortality.

The current gold standard in treatment of conflict-related wounds relies on experiences gained from armed conflict zones of the past century. Treatment includes initial wound debridement, followed by the application of a dressing to absorb excess fluid and protect the open wound from further contamination, until reassessment and, if possible, delayed wound closure in the operating theatre 3–5 days later.[8,9]

In negative pressure wound therapy (NPWT), the wound is covered, and negative pressure is applied. Expert consensus has suggested NPWT as an alternative to the gold standard treatment of traumatic wounds.[10] Although NPWT has been used since the 1990s for

Research in context

Evidence before this study

A systematic review of negative pressure wound therapy (NPWT) from 2018 found a high risk of bias with respect to random sequence generation and use of unclear or inappropriate endpoints. These factors substantially reduced the credibility of most of the 93 included randomised trials. Additionally, a 2018 Cochrane review of NPWT for open traumatic wounds was inconclusive regarding healing rate and risk of infection. We searched PubMed on Feb 11, 2019, for the terms "negative pressure", "vacuum assisted", and "vacuum dressing", with no language or date restrictions. We did not identify any comparative trials from armed conflict settings, nor any additional randomised trials on NPWT for traumatic wounds that had not already been included in the Cochrane review.

Added value of this study

We report the results for the first randomised controlled trial designed to assess the effectiveness of NPWT in the treatment of acute conflict-related extremity wounds. NPWT did not significantly increase the number of patients achieving wound closure by day 5, and it did not provide net clinical benefit compared with standard treatment. We used a rigorous design with appropriate endpoints and reporting. An additional benefit of this study is that it was done in settings with scarce resources for trauma care.

Implications of all the available evidence

Existing evidence supports our concerns that introducing increasingly technically complicated and costly treatments without clinically important evidence could reduce the quality of trauma care in resource-limited settings. We question the increasing use of NPWT for traumatic extremity wounds, irrespective of available resources.

chronic or complicated wounds,[11] little evidence suggests that it promotes wound healing. Two systematic reviews[12,13] concluded that the credibility of previous studies is substantially reduced because of poor study quality, low statistical power, or a high risk of bias with respect to random sequence generation, and use of inappropriate endpoints.

In the case of traumatic wounds, few randomised trials have been done, and all from non-conflict settings. Investigating differences in time to closure, risk of wound infection, and adverse events between NPWT and standard care, these studies have yielded mixed and conflicting evidence.[13] Despite this finding, NPWT has been introduced as a treatment option for patients with conflict-related injuries, even in resource-limited settings, regardless of its additional costs. Therefore, we did a randomised controlled trial to compare the safety and effectiveness of NPWT against that of standard wound treatment, specifically in patients with acute conflict-related extremity wounds.

For the **trial protocol** see www.researchprotocols.org/2018/11/e12334

Methods

Study design

This is a pragmatic, randomised, controlled superiority trial, done at two civilian trauma hospitals in Jordan and Iraq. The study started at a hospital in Ar Ramtha, Jordan. The hospital is located close to the Syrian border and is supported by the international non-governmental organisation, Médecins Sans Frontières. At this hospital, patients receive treatment for conflict-related injuries sustained in Syria. Temporary closure of the Syrian border in June 2016 led to enrolment difficulties and, consequently, the trial was expanded to include a hospital in Erbil, Iraq. This hospital is run by the local non-governmental organisation, Emergency Management Center, and received patients from Mosul during the armed conflict in 2016–17.[14] When the Syrian border was reopened in November 2016, patient enrolment in Jordan was resumed but was suspended again in February 2017.

Ethics approval for the study was obtained from the Ethics Review Committee of the Jordan Ministry of Health (MOH REC 150037), the Ethics Review Board of Médecins Sans Frontières (ID 1520), the Research Ethics Committee of Kurdistan Regional Government in Iraq (2:10 6/3/2017), and the Swedish Ethical Review Authority (2019–01975). All trial procedures adhered to the Declaration of Helsinki and guidelines for Good Clinical Practice. Additionally, an external monitor regularly reviewed unmasked data in confidence. The study design and methods have been described elsewhere.[15] The trial protocol is available online. The trial is registered with ClinicalTrials.gov, NCT02444598.

Participants

Patients eligible for study participation had to be aged 18 years or older, and they had to present at the emergency department within 72 h of sustaining a conflict-related extremity wound. Patients with a wound deemed suitable for primary closure (eg, small or superficial) were not included. All participants gave written informed consent. Because acutely injured patients are often not fully conscious when being transported from the emergency department to the operating theatre, the principle of delayed consent was used. Thus, those patients entered the study under presumed consent. Informed consent for their continuation as participants in the trial was then collected at the first appropriate opportunity, within 5 days of their random allocation. Patients not able to give consent by day 5 were excluded from the study.

Randomisation and masking

Participants were randomly assigned (1:1), via a computer-generated randomisation code with random variation of three fixed block sizes (4, 6, 8) to receive either NPWT or standard treatment. An investigator with no clinical involvement in the trial prepared the allocation sequence. The sequence was concealed from researchers responsible for enrolling and assessing participants. The attending surgeon determined eligibility and enrolled the participants. The sequentially numbered, opaque, sealed randomisation envelopes were kept in an agreed location in each operating theatre. To enter a patient into the study, the operating theatre nurse opened the next consecutively numbered envelope at the end of the primary surgery, but before the wound dressing was applied. Participating staff, patients, and researchers were not masked to treatment allocation. Wounds were photo-documented, and photographs were assessed by two independent clinicians who were masked to treatment allocation.

Procedures

NPWT dressings involved the application of sterile, open-cell, solid foam covered by a plastic film, through which a negative pressure was applied. This technique enables blood and fluid to be drained from the area, while keeping the wound moist. A professional NPWT device (Conformité Européenne) was used, with a continuous negative pressure of 125 mm Hg (in Jordan, we used Vacuum Assisted Closure by KCI, San Antonio, TX, USA; in Iraq, we used Fava by EZM, Ankara, Turkey).

Standard wound dressings were applied in accordance with the International Committee of the Red Cross war surgery protocols.[9] These dressings were non-adhesive sterile gauze covered with a bandage, applied at the discretion of the treating surgeon.

All participants received prophylactic treatment with cefazolin or amoxicillin plus clavulanic acid. Metronidazole or gentamicin was added for patients with open fractures. Fractures were immobilised by external fixation. The treating surgeon changed the dressings in the operating theatre every 3–5 days and did further wound debridement if needed. Participant follow-up occurred at each dressing change, at hospital discharge, at days 14 and 30, and at 3 months following day of randomisation.

Outcomes

The prespecified primary endpoint (effectiveness) was wound closure by suture, flap, or split-thickness skin graft, within 5 days from initial debridement surgery. The prespecified coprimary endpoint (safety) was net clinical benefit, defined as a composite of wound closure by day 5 and freedom from any bleeding, wound infection, sepsis, or amputation of the index limb. In this paper, we report the prespecified secondary endpoint of time to wound closure. In case of closure failure, time to final closure was recorded. We also report the prespecified safety endpoints of wound infection (defined as purulent discharge), sepsis, bleeding leading to blood transfusion, amputation of the index limb, and death. The incidence, nature, and severity of adverse events were assessed in all participants by the research team.

The other secondary endpoints, which will be reported elsewhere, were: wound size ratio at day 14; time until wound is deemed no longer requiring professional care; number of surgeries; time to hospital discharge; quality-of-life aspects; wound healing at follow-up days 14 and 30, and at 3 months; direct health-care costs (substudy); and cost-effectiveness (substudy). We used patient-centred endpoints and follow-up periods as suggested by the US Food and Drug Administration.[16] Definitions have been reported elsewhere.[15]

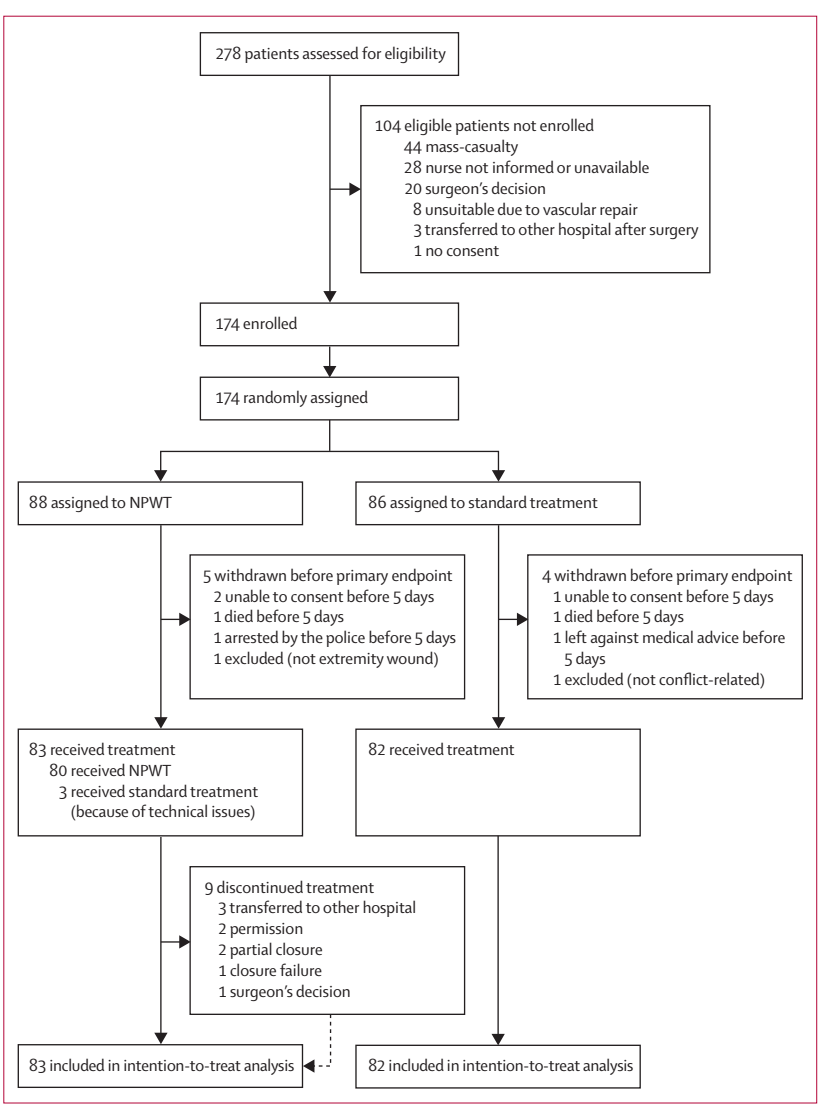

Figure 1: **Trial profile**
NPWT=negative pressure wound therapy.

	NPWT group (n=83)	Standard treatment group (n=82)
Sex (male)	77 (93%)	78 (95%)
Age (years)	28 (21–33)	29 (22–35)*
Currently smoking	55 (66%)	51 (62%)
Diabetes	0	1 (1%)
Other disease	7 (8%)	6 (7%)
Time from injury to admission <48 h	82 (99%)	81 (99%)
Surgery before admission	7 (8%)	7 (9%)
Pulse rate on admission (beats per min)†	98 (88–110)	92 (84–110)
Systolic blood pressure on admission (mm Hg)‡	120 (108–130)	125 (110–134)
Haemoglobin level on admission (g/L)§	13·3 (11·3–14·3)	13·0 (11·3–14·7)
Multiple wounds	68 (82%)	69 (84%)
Concomitant injuries		
Penetrating injury to the brain or spinal cord	0	0
Penetrating injury to the abdomen	4 (5%)	6 (7%)
Penetrating injury to the thorax or trachea	2 (2%)	4 (5%)
Brain injury	0	0
Lung injury	1 (1%)	0
Heart injury	0	0
Injury of abdominal solid organ or GI tract	3 (4%)	4 (5%)
Urogenital injury	3 (4%)	3 (4%)
Concomitant fracture	19 (23%)	14 (17%)*
Any concomitant injury	24 (29%)	19 (23%)
Wound localisation		
Upper extremity	20 (24%)	26 (32%)
Lower extremity	63 (76%)	56 (68%)
Injury mechanism		
Blast	32 (39%)	31 (38%)
Gunshot	51 (61%)	49 (60%)
Other	0	2 (2%)
Wound area (cm²)	40·0 (16·1–107·7)*	27·5 (6·0–81·0)
Fracture at site of studied wound	43 (52%)	31 (38%)*
Injury to major blood vessel	9 (11%)	5 (6%)
Bone exposed	40 (48%)	22 (27%)
Tendon exposed	40 (48%)	31 (38%)
Nerve exposed	38 (46%)	21 (26%)
Metallic body	24 (29%)	21 (26%)

Data are n (%), median (IQR). NPWT=negative pressure wound therapy. GI=gastrointestinal. *Data missing for one participant. †Data missing for seven participants in the NPWT group and for six participants in the standard treatment group. ‡Data missing for eight participants in the NPWT group and for seven participants in the standard treatment group. §Data missing for four participants in the NPWT group and for three participants in the standard treatment group.

Table 1: **Baseline characteristics of the intention-to-treat population**

For more on the **R software** see https://www.r-project.org/

Statistical analysis

We based the target sample size on the assumption that 75% of participants in the NPWT group would reach the primary endpoint by day 5, compared with 50% of participants in the control group (these calculations were based on a review of the literature and discussions with medical doctors with experience from conflict-related trauma care). We calculated that 58 participants per treatment group, at a significance level of 5%, would give the study 80% power. Considering the nature of the study setting, we anticipated higher dropout levels than might be expected in other trials. To adjust for dropouts, we therefore aimed to recruit 200 participants (100 per group).

Analysis was done on the intention-to-treat population. No interim analyses were done. Continuous variables are reported as median (IQR), whereas categorical variables are reported as numbers and proportions. Between-group differences in categorical variables were compared with Fisher's exact test. We calculated two-sided 95% CIs for absolute differences in the proportions of outcomes, according to the method of Jeffreys.[17] We estimated time to closure with the Kaplan-Meier method, and used the Mantel-Haenszel log-rank test to compare Kaplan-Meier cumulative incidence curves. A standard Cox proportional hazards model was used for estimating the relative chance of closure (hazard ratios [HRs] and 95% CIs), with the standard dressing group used as the reference. Furthermore, inspection of log–log plots and a global test based on Schoenfeld residuals indicated that the proportional hazards assumption was not violated. A two-sided p value of less than 0·05 was considered to indicate statistical significance. We did statistical analyses with R version 3.5.0 software.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 9, 2015, and Oct 24, 2018, 174 participants were enrolled, of whom 88 were randomly assigned to receive NPWT and 86 to receive standard treatment (figure 1). Two participants, one from each treatment group, were excluded after randomisation because they were found to be ineligible. Due to cognitive impairment, two participants from the NPWT group and one from the standard treatment group were unable to provide delayed consent after randomisation. Two participants, one from each group, died within 5 days; one from the standard treatment group left against medical advice, and one participant in the NPWT group was arrested by the police, both within 5 days. Consequently, 165 participants with data on primary outcome (83 in the NPWT group, 82 in the standard treatment group)

were included in the intention-to-treat analysis. Table 1 summarises the study population characteristics at baseline. The groups were well balanced in baseline characteristics, except for wound area and proportion of participants with exposed bone and vital structures.

The proportion of participants with wound closure by day 5 was not significantly higher in participants treated with NPWT than in those receiving standard treatment (41 [49%] of 83 *vs* 49 [60%] of 82 participants), with an absolute difference of 10 percentage points (95% CI –5 to 25, p=0·212), and a risk ratio (RR) of 0·83 (95% CI 0·62 to 1·09; table 2). Furthermore, the difference in net clinical benefit between the NPWT and standard treatment groups was not significant (33 [41%] of 81 *vs* 34 [44%] of 78 participants), with an absolute difference of 3 percentage points (95% CI –12 to 18, p=0·750; RR 0·93, 95% CI 0·65 to 1·35). Median time to wound closure was 5 days (IQR 4–11) in the NPWT group and 5 days (4–8) in the standard treatment group (figure 2). It should be noted that for the time-to-wound-closure analysis, four participants were not included (two had amputations [one in each group], one died in hospital [standard treatment group], and one was lost to follow-up [standard treatment group]).

Treatment with NPWT did not increase the chance of wound closure (HR 1·09, 95% CI 0·80 to 1·50; p=0·584; figure 2). This finding remained after adjustment for imbalances in wound area, fracture at site of the studied wound, injury to major blood vessels, and exposed bone, nerve, or tendon (HR 1·17, 95% CI 0·82 to 1·65; p=0·385). Furthermore, net clinical benefit did not increase with NPWT (HR 0·90, 95% CI 0·56 to 1·45; p=0·750).

Primary endpoint data were available for all 165 participants. Blinded review of available wound photographs for the primary endpoint did not result in any changes to the initial assessments.

Wound infection was diagnosed in ten (12%) of 83 participants in the NPWT group, and 19 (23%) of 82 participants in the standard treatment group, with an absolute difference of 11 percentage points (95% CI –0·5 to 23, p=0·068; RR 0·52, 95% CI 0·26 to 1·05; table 2). The proportion of participants with sepsis, bleeding leading to blood transfusion, and limb amputation did not differ between groups. There was one in-hospital death in the standard treatment group and none in the NPWT group (table 2).

Minor deviations from the protocol occurred. For example, participants were assigned to NPWT, but treatment initiation was delayed (n=4) or treatment progress was paused (n=3). In five participants, the attempted wound closure failed; their times to final wound closure were recorded.

	NPWT group (n=83)	Standard treatment group (n=82)	Absolute difference	RR (95% CI)	p value*
Wound closure by day 5	41/83 (49%)	49/82 (60%)	10 (–5 to 25)	0·83 (0·62 to 1·09)	0·212
Days to wound closure†	5 (4–11)	5 (4–8)	..	..	..
Net clinical benefit‡	33/81 (41%)	34/78 (44%)	3 (–12 to 18)	0·93 (0·65 to 1·35)	0·750
Safety endpoints	..	..	..	..	..
Wound infection	10/83 (12%)	19/82 (23%)	11 (–0·5 to 23)	0·52 (0·26 to 1·05)	0·068
Bleeding	32/81 (40%)	24/78 (31%)	9 (–6 to 23)	1·28 (0·84 to 1·97)	0·319
Sepsis	1/83 (1%)	4/82 (5%)	4 (–2 to 10)	0·25 (0·03 to 2·16)	0·210
Amputation	1/83 (1%)	1/82 (1%)	0 (–4 to 4)	0·99 (0·06 to 15·53)	1·00
In-hospital death	0/83	1/82 (1%)	1 (–2 to 5)	0·33 (0·01 to 7·97)§	0·497
Any safety endpoint	26/81 (32%)	34/80 (43%)	10 (–4 to 25)	0·76 (0·50 to 1·13)	0·194

Data are n/N (%), median (IQR), or percentage points (95% CI). NPWT=negative pressure wound therapy. RR=risk ratio. *From Fisher's exact test. †Four participants not included; two had amputations (one in each group), one died in hospital (standard treatment group), one was lost to follow-up (standard treatment group). ‡Composite of wound closure by day 5 and freedom from any bleeding, wound infection, sepsis, or amputation. §Haldane-Anscombe correction.

Table 2: **Clinical outcomes for the intention-to-treat population**

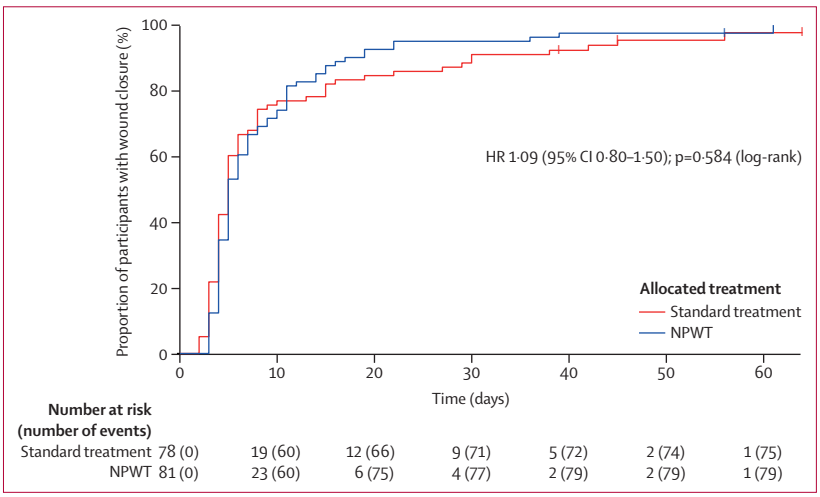

Figure 2: **Probability of wound closure (Kaplan-Meier estimate) over time from randomisation**
Standard treatment is reference. HR=hazard ratio. NPWT=negative pressure wound therapy.

Discussion

In this multisite trial in patients with acute conflict-related extremity wounds, NPWT did not improve prevalence of wound closure by day 5, nor time to wound closure compared with standard treatment. No significant difference was seen in net clinical benefit, defined as a composite of wound closure by day 5, and freedom from any bleeding, wound infection, sepsis, or amputation of the index limb. In addition, we found no significant differences between the groups in prevalence of in-hospital death, nor in complications such as wound infection, sepsis, or amputation.

Previous randomised trials have compared NPWT with standard wound dressing for traumatic extremity wounds in non-conflict settings and yielded disparate results. Virani and colleagues[18] studied open diaphyseal tibial fractures in 93 participants and found evidence of reduced prevalence of infection using NPWT, but no reduction in time to closure. Arti and colleagues[19] assessed NPWT in 90 participants with open fractures, treated at a university hospital, and found it to be superior in

prevalence of wound healing; however, they reported no significant difference in incidence of infection. Stannard and colleagues[20] found evidence of NPWT reducing rate of deep wound infection in 59 participants with severe open fractures who were treated at a level 1 trauma centre, but they did not report any data on wound closure. Costa and colleagues[21] assessed NPWT (n=460) for open lower-limb fractures after mainly road traffic accidents in a high-resource setting and found no difference in the primary outcome of self-rated disability after 12 months, nor in secondary outcomes of wound healing and infection rate. Taken together, these trials have yielded contradictory findings on NPWT for traumatic wounds. Use of this technique in the treatment of blast and gunshot wounds has previously not been studied.

To our knowledge, this study is the first randomised trial done in resource-limited settings close to armed conflict. We acknowledge the challenges involved in doing research in such settings, particularly in terms of access, security for participants and researchers, and data collection and management. However, this study shows that most of these challenges can be overcome with appropriate study design and a dedicated research team.

This pragmatic study has several limitations. First, the wounds were larger in the NPWT group, and prevalence of exposed bone and vital structures was higher than in the standard treatment group. However, adjusting for these imbalances did not affect the findings. Second, nine participants were lost before day 5, reducing data required for the primary endpoint. However, these losses were not related to allocated treatment and would therefore not cause bias. Third, absence of participant and personnel masking could have introduced bias. We minimised this risk by using rigorous design and random sequence generation, allocation concealment, masked review of wound photographs, and appropriate endpoints. Finally, the anticipated treatment effect underlying a power calculation can always be questioned. We used a difference of 25%, as this was deemed clinically relevant, given the anticipated higher costs for NPWT than for standard treatment. Furthermore, randomised trials of NPWT for various indications have claimed effect sizes of up to 48%.[20,22,23]

The strengths of this study include the multisite design, a real-world setting with hospitals located in proximity to armed conflict, and independence from any company involvement. Furthermore, participant enrolment reached the intended target and dropouts were fewer than expected. Consequently, we obtained power in excess of the calculated 80%. We were able to randomise more than 60% of the eligible population and we believe the participants are representative of civilians with extremity injuries from armed conflict areas. Therefore, our results are likely to be generalisable to other populations of injured civilians.

Conflict-related extremity injuries are a major concern in the civilian population. In Syria alone, an estimated 86 000 people are living with amputations due to injuries sustained in the ongoing armed conflict.[24] Our results challenge the introduction of NPWT for civilians with conflict-related injuries. This technique is expensive and requires substantial resources that could be better spent on other efforts. We acknowledge the need for high-quality research before introducing new treatment protocols, especially in settings where resources are scarce. Our study not only adds new knowledge to the treatment of conflict-related extremity injuries, it also shows that doing robust civilian research close to a conflict zone is feasible. We hope to encourage further research in this area to generate evidence on which to base treatment protocols for civilian casualties in armed conflicts.

In this multisite, randomised trial, NPWT did not reduce time to wound closure and incidence of wound infection in patients with acute conflict-related extremity wounds. As the evidence does not support NPWT for traumatic extremity wounds, clinicians treating such injuries should continue to use standard treatment for wound care.

Contributors

AÄ, JM, JvS, KCL, and SW designed the study. AÄ initiated and oversaw the trial at the study sites. RH contributed to patient enrolment, treatment, and data collection. KB provided administrative support. AÄ and JM analysed the data. AÄ wrote the first draft. JM, JvS, KCL, SW, RH, and KB were major contributors in writing the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

We declare no competing interests. This is an investigator-initiated trial. No companies were involved in any part of the trial, nor did any companies contribute funding.

Data sharing

Individual participant data that underpin the results reported in this Article will be made available, after their deidentification, alongside a data dictionary, study protocol, and informed consent form. Data will be available with publication and for 10 years subsequently. Data will be shared for individual-participant-data meta-analysis with other members of the research community who have an affiliation to a recognised medical university. Data will only be shared with investigator support, after approval of a proposal, and with a signed data access agreement. Additional restrictions will apply in accordance with Swedish law. Proposals should be directed to andreas.alga@ki.se.

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