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REVIEW

Hypnosis for burn-related pain: Case studies and a review of the literature

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Abstract

Burn injuries create severe pain and psychological distress that are highly variable between patients. Distinct types of pain during various stages of injury and recovery make treatment complex. Standard pharmacological treatment of pain can have adverse effects and is not effective in treating anxiety and other psychological issues. Researchers have proposed that integrating clinical hypnosis as a complementary therapy can be highly beneficial to burn patients and their healthcare providers. The existing literature is reviewed and specific hypnosis techniques are discussed. Evidence exists indicating that adjunctive hypnosis is effective at reducing pain and procedural anxiety. Implementing a multidisciplinary burn care team that includes clinical hypnosis and focuses on the patients' psychological health as well as pain reduction is likely to result in faster healing and reduced distress for patients and caregivers alike.

Key words: Hypnosis; Burns; Burn units; Complementary therapies; Anesthetic hypnosis

Core tip: After a burn injury, patients can suffer from severe pain and psychological distress with high variability between patients. Standard pharmacological treatment of pain may have adverse effects and may not be effective in treating psychological issues. Evidence indicates that adjunctive hypnosis and a focus on patients' psychological health as well as pain reduction is effective at accelerating recovery, reducing

pain, and decreasing procedural anxiety. Information on clinical hypnosis as well as specific hypnosis techniques and suggestions for analgesia are discussed herein.

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INTRODUCTION

Pain that accompanies burn injuries can be severe, relentless, and have high variability between patients[1,2]. With burn injuries, the tissue damage alone amounts to high levels of pain. However, repetitive wound care, dressing changes, and rehabilitation therapies after initial injury are likely to exacerbate the already painful experience[1,2]. The psychological needs of the patients, just as their analgesic requirements, evolve with the variability of their pain and recovery. Psychological concerns such as anxiety, depression, and poor body image are frequently reported[3-6]. These factors in combination make the treatment needs of burn patients very complex from initial care to rehabilitation.

Burn pain is multifaceted, with several different types of pain present throughout the treatment, such as background pain, procedural pain, breakthrough pain, pain due to hyperalgesia, allodynia, and chronic pain[1,7-9]. Though burn injuries are classified according to size and thickness of area harmed, the pain experienced by patients does not necessarily correlate highly with their classification[8]. Though nerve damage seen with deeper burns theoretically reduces pain felt, clinical observations contradict this theoretically valid expectation[10]. Additionally, there are considerable personal differences in the level of pain reported even with the wound classified to be similar[8]. The unreliability of the injury in informing us about actual pain levels makes communication with patients throughout treatment and rehabilitation crucial.

It is important to note that aside from the anguish experienced by the patient, poor pain control has several harmful consequences. There is a correlation between pain experience, length of hospital stay, and long-term emotional well-being[1,8]. Not only can anxiety worsen the experience of pain, but pain experiences may interfere with physical and psychological healing[1,2]. Studies have shown that when a distressing procedural pain experience induces fear and anxiety, pain perception increases as well as poor compliance in future therapies[11]. When acute burn pain is uncontrolled, the rates of depression, chronic pain, and post-traumatic stress disorder increase[12-14]. Overall, if pain control is ineffective, many issues can arise due to an increase in the patient's stress response[15,16]. Drugs such as opioids, ketamine or anxiolytics are generally the initial treatment for pain inflicted by tissue damage. Though drugs can lessen the intensity of the pain for some patients, they may not create a change in the psychological aspects of burn injuries. Use of medications for pain can produce several side effects such as, respiratory depression, nausea, and itching at the burn site[8].Overuse of opioids can also lead to tolerance, ineffectiveness, and hyperalgesia.

Because burn patients have complex care needs and highly variable symptoms, there is a need for a personalized care. Experts in the field agree that integrative, non-pharmacological treatments should be considered as a complement to conventional treatments in order to reduce total drug use and ensure the best possible care[2,17]. This article will discuss hypnosis in clinical practice, introduce how hypnotic techniques can be applied to burn care, review research that has examined hypnosis for burn care, and review possible mechanisms and mediators of hypnosis treatments.

COMPLEMENTARY TREATMENTS

It is imperative that care centers be knowledgeable in complementary options that can be incorporated to target issues unique to each patient. There are well-established nonpharmacological ways to care for those suffering from pain that are already in use. This includes keeping wound dressing changes to the minimum necessary, using limb elevation, properly soaking dressings, and communicating well with the patient. Using calm actions and voices can provide further comfort during wound care.

Complementary therapies including virtual reality (VR)[2,6,18], cognitive-behavioral therapy (CBT)[19-21], and hypnosis[22-33] may help patients cope before, during or after painful procedures. While interventions like VR and CBT are potentially beneficial, there are challenges associated with implementing them. Over 95% of burn injuries from fire occur in middle to low-income populations[34], yet VR equipment is expensive and unlikely to be used in areas of poverty. VR equipment also usually involves a helmet for the mounted display system[2] which may be difficult or impossible to use with patients who have burns on their head or face. Though possibly advancing to additional sensory immersions in the future, VR experiences are most commonly visual, so seeing impaired patients may not benefit as much from this technology. In reviewing treatments for acute and procedural pain, Stoelb *et al*[35] found that compared to behavioral and control interventions, hypnosis provided greater or equal pain reductions in all of the trials. Treatments such as CBT and relaxation training did not exceed hypnosis in efficacy, with hypnosis resulting in greater pain reductions in approximately half of the cases[35]. Due to these findings and limitations, interest in clinical hypnosis for burn care has increased.

HYPNOSIS IN CLINICAL PRACTICE

Hypnosis is defined as a "state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion"[36]. Hypnosis in clinical practice, sometimes referred to as hypnotherapy, is the "use of hypnosis in the treatment of a medical or psychological disorder or concern"[36]. One of the central characteristics of hypnosis is that the responses individuals have to suggestions feel effortless and automatic[37]. Hypnosis in clinical practice is versatile in that it can be used in the form of live presentation or pre-recorded audio, though live delivery is generally preferred if possible[38] and may be more effective.

Hypnosis is sometimes overlooked as a viable treatment option for medical issues[39]. However, clinical hypnosis may be an effective treatment or treatment complement for numerous illnesses and disorders including depression, anxiety, phobias, stress, smoking cessation, gastro-intestinal disorders, pain, sexual functioning, surgical recovery, and nausea[40-42]. The efficacy of clinical hypnosis for pain and procedural anxiety has been well supported through numerous studies[38,43-46], though more research specific to burn pain is needed. Because of the success of this research and evidence that hypnosis can reduce costs[47] as well as pain severity and frequency, interest in hypnosis for managing pain has grown in recent years[45].

HYPNOSIS IN THE STAGES OF BURN CARE

The versatility of hypnosis allows for it to be applied in all stages of burn care. For instance, hypnosis programs may involve a practitioner-led hypnotic induction with calming suggestions prior to painful procedures such as debridement and wound care. In this case, the main objective is to prepare the patient for the painful and anxiety-inducing procedure in a quieter setting. Hypnosis or hypnotic analgesia can be used during the painful medical treatments as well to take the patient's attentional focus away from the painful stimuli and create a sense of comfort[18,27]. Beyond hypnotic suggestions for analgesia and calmness, the therapist may want to suggest that time is passing quickly during the procedure[48]. Hypnosis can also be used during the rehabilitation and recovery phase, when suggestions for faster healing are generally given[23,25].

Post-hypnotic suggestions and the practice of self-hypnosis offer a solution for the long lasting nature of burn pain, allowing for the specific suggestions for pain reduction or relaxation to remain after the session is over. In post-hypnotic suggestions, instructions may be given for the individual to use a mental cue such as deep breathing or focused attention, to create a calm state when needed. Hypnosis can also be applied by the patient without the presence of the hypnotherapist through the use of recordings or by learning self-hypnosis. This approach might be especially useful for patients suffering from chronic pain[45].

HYPNOSIS TECHNIQUES AND SUGGESTIONS FOR BURN CARE

Induction techniques may vary and can include an arm-levitation technique, eye-focus, eye-closing, or a cenesthetic technique, which is an inward focused attention to a bodily sensation[32,33,48]. Deepening of hypnosis is usually done by guided imagery, glove anesthesia (an essential technique used in hypnotic analgesia, especially for procedural pain. This involves suggestions for loss of sensation in the patient's hand, as if they were wearing a thick glove. The therapist can then use a pen to stick the patient's finger, and have the patient open their eyes and see that though they cannot feel it, there is something sticking their finger. This serves the purpose of pain control as well as a demonstration of the power of their mind's ability to block pain. The anesthesia can then be transferred to a painful body parts as needed[48]), counting, suggestions for progressive relaxation of muscles, or dissociation[32,39]. There is no single formula for hypnotic induction and most techniques can be used in conjunction with others.

Hypnosis for pain relief can include suggestions such as "feelings of pressure but no pain", coolness, comfort, and numbness[48]. Suggestions for removing all pain are not generally recommended, but "minimal pain" or "discomfort" will ideally leave the patient with enough awareness of the area without any distressing pain[48]. Using imagery in a hypnotic induction can be an additional way to deepen the experience and allow a patient suffering from burns to feel as though they are in a snowy forest or a cold bath[24].

As mentioned before, pain is not the only symptom to keep in mind when treating victims of burns. Crasilneck *et al*[48] report on an induction that has proven successful in improving food intake in patients who refuse to eat for various reasons. Suggestions used include "you are going to be able to definitely increase your food intake", and "you will enjoy your food… realizing that with every mouthful you digest you are improving your physical and mental state".

Exercising treated areas is essential to proper healing, but many patients who are in pain are apprehensive of creating more pain by exercising. Hypnotic suggestions such as "You can and will exercise your hand for 15 min out of each waking hour, as prescribed by your doctor" and "There will be minimal, if any, discomfort" can also be applied to encourage proper exercise[49].

Hypnotic suggestions are generally individualized to meet each patients' preferences for mental imagery. However, it is important to note that most hypnotic inductions for pain management include suggestions for focus of attention, eye-lids closing, then deepening

by counting and muscle relaxation, then suggestions for coolness or analgesia, and include suggestions for specific treatment goals (*e.g.*, anxiety reduction, pain relief).

Compared to standard treatment, hypnosis is generally exceptionally helpful in relieving anxiety which may be keeping patients from healing as quickly as they could[22]. Suggestions for relaxation and calmness are commonly used and posthypnotic cues are a great way to ensure that relaxation continues beyond the hypnotic state[39,50].

EFFICACY OF HYPNOSIS FOR BURN PAIN AND ASSOCIATED SYMPTOMS

In order to assess the effectiveness of using hypnosis in burn care, a review of the clinical studies was conducted and is presented here. Case studies and published clinical observations are included to illustrate the history of including hypnosis in burn care, as well as varying methodologies. Controlled studies are then reviewed to evaluate the evidence for the use of hypnosis for burn pain.

In order to fully review the literature, the keywords and keyword combinations "hypnosis", "hypnotherapy", "burn care", "burn wounds", "debridement", and "pain" were used in searches through PsycINFO, PsycARTICLES, MEDLINE, PubMed, and Google Scholar. Additional articles were then selected from the references of the retrieved literature. All studies, whether experimental, quasi-experimental, or non-experimental, that investigated efficacy of hypnosis to manage pain, distress, and associated symptoms were included in the article.

Case studies and case series

Much of the early research on hypnosis for burn pain was in the form of clinical case studies. One of the first reports of hypnosis as an aid to pain management for burn injuries came in 1955[50]. The patient was a young adult woman with a 90% total body surface area (TBSA) affected by second and third degree burns. She was experiencing non-stop, severe pain and was in fear. Through hypnosis, she was able to experience calmness, a reduction in anxiety, and relief from most of the pain. Despite the medical team's best efforts, the patient died 3 d after the injury. However, the use of hypnosis allowed her minimal suffering after a terrible and frightening injury.

Hypnotherapy was then used to reduce pain, increase appetite, and instill calmness for a 24-year-old male patient whose burns and resulting complications had led to his refusal to eat or attempt to leave his bed[49]. Within a few days of treatment, the patient was eagerly eating sufficient amounts at each meal, though previous attempts at coercion, long explanations of importance, and force feeding through a tube had all failed to stop his weight loss. Six weeks after the start of hypnosis treatment he was eating well, exercising regularly, and skin grafting procedures that had previously been consistently unsuccessful were at a 90% success rate. After his attitude and social behavior improved markedly, narcotics were discontinued and he reported no complaints of pain. This case highlights the potential benefits of hypnosis in clinical practice. The integration of hypnosis into treatment benefitted the patient in multiple ways including improvements of attitude, appetite, anxiety, motivation, and pain.

Crasilneck *et al*[49] describe the case of a 33-year-old man who was experiencing fear and apprehension due to extremely painful skin grafting procedures. Though general anesthesia was used during dressing changes, he regularly complained of pain after each treatment. For the first 30 d after the injury, the anxiety and pain had caused him to refuse to exercise his hands, which is necessary for healing. Using this first month in the hospital as a control, hypnosis was then used as the analgesia for wound treatments. After no discomfort was reported, hypnotic anesthesia was used during a split-thickness skin graft with posthypnotic suggestions that he would regularly exercise his hands and for no pain in the donor area. After the treatment, he reported a lack of feeling in the donor area. Three days later, the patient was exercising his hand so regularly that subsequent hypnotic suggestions had to be made so that he would only exercise when he was awake. Benefits of this case study were listed as avoidance of narcotics and repeated anesthetics as well as the patient's new willingness to exercise.

In another case, hypnosis was again shown to dramatically lower use of narcotics. A male patient with a 35% TBSA affected by burns received hypnosis upon hospital admittance, about four hours after original injury[48]. In this case, no narcotics were needed during the patient's first 18 d in the hospital, which included many painful procedures. Hypnosis was used throughout his stay to relieve pain.

Thus far, the research mentioned here has reported results for adult patients, but hypnosis may be beneficial for children as well. Bernstein[51,52] described clinical observations of the effect of hypnosis suggestions on pediatric burn victims and the therapists and staff caring for them. It was concluded that hypnosis seemed to be beneficial for helping children who were depressed or isolated. Improvements seen in the children also included higher pain tolerance, improved appetite, increased cooperativeness, and better mood. Providing children with the integrated hypnosis also led to an improvement in morale for their healthcare providers.

Ewin[53-56] observed that the use of hypnosis in emergency room settings can block burn pain from reaching excruciating levels and can expedite healing of burn wounds. Throughout his research, Ewin[53-56] emphasizes that hypnosis should be implemented as soon as possible post-injury in order to achieve the best results. In one case, a man who was injured after stepping into molten metal to the knee, received hypnosis within four hours of injury[56]. The burns he

developed were second-degree and his hospital stay was 3 wk long, which were both better outcomes than expected. It was concluded that the hypnosis not only aided in relieving his pain, but also may have decreased swelling and increased blood flow to the injured site.

In another case study, it was reported that after an explosion on a United States Navy ship, hypnosis was used to calm an adult patient to enable intubation and as an adjunct to trauma care[57]. As in Ewin's research mentioned above, hypnosis was delivered as soon as possible. Specific suggestions were made for decreased anxiety and quick healing. The authors argue that not only can hypnosis aid in treating pain, but can also lessen the patient's perception of severity of the situation. Improving the patient's well-being during rehabilitation leads to avoidance of many negative stress effects.

A case study involving an adult male in an intensive burn care unit highlights the utility of hypnosis when there are adverse effects from standard pain medications[58]. After a chemical burn, the patient (265 lbs, 120 kg) was admitted to the burn unit and given 100 μg of fentanyl for pain during first wound treatment. He quickly developed a sinus tachycardia and was overly sedated even hours later into the next morning. The next day fentanyl was administered 50 μg at a time for a total of 2250 μg and the patient developed respiratory depression and hypotension. The opioid dosages the patient received were below average as compared to patients with similar injuries in this care unit and his pain was inadequately controlled, yet he was experiencing multiple side effects. Barber's[59] rapid induction analgesia (RIA) was then used during treatments, accompanied by little to no drugs. Outcome measures were a numeric pain scale and amount of pain medication and anxiolytics used. Pain scores decreased, no supplemental anxiety medication was needed, the wound care period was shorter than expected, and staff responses were positive. The authors note that the hypnotic analgesia treatment was implemented easily in the hectic hospital setting, and it was extremely beneficial for a patient who reacted negatively to conventional medications.

In order to minimize peripheral stimuli and make hypnotic analgesia easier for patients to focus on, some researchers are delivering hypnosis with the help of VR technology. In one of the first clinical case series to use this technique, pain scores before and after treatment procedures were collected for 13 patients[18]. The hypnosis intervention involved a VR environment in a snowy canyon with recorded hypnotic instructions. Though five patients were dropped from the study prior to final data collection due to changes in care plans, data from 8 patients revealed that self-reported pain and anxiety decreased and there was a 50% decrease in opioid use from baseline to day three. Hypnotizability scores were assessed, and the correlation with pain was not significant. Therefore, patients benefitted from the treatment regardless of their ability to respond to hypnotic suggestions, so this technique is likely applicable to a wide patient population.

In the cases presented here, patients all responded at least to some extent to clinical hypnosis, and most of them had very favorable responses. In addition to pain relief, improved motivation, and anxiety relief, some studies also reported improvement in recovery time and a decrease in pain medications. It should be further investigated whether these additional benefits are the result of the application of hypnosis. It is also encouraging that there were no mentioned side effects or adverse reactions to the hypnosis interventions used. Though generalization is not guaranteed, the results from these case studies and case series evidence the value of hypnosis for this population.

Controlled trials

There have also been several controlled studies examining the use of hypnosis as an adjunct treatment for burn injuries and associated symptoms. These studies are summarized in Table 1. In one of the first controlled studies to research hypnosis for burn pain, 42 participants of ages ranging from 7 to 70 with an average burned TBSA of 60% were assigned to either a hypnosis group or a standard care control group[22]. Hypnosis sessions were therapist-guided during painful procedures. The therapist then met with each patient regularly for training in self-hypnosis until the patient demonstrated confidence in doing so. Depending on what worked best for each patient, different induction techniques were used for those in the treatment condition including eye-fixation, eye-roll, and progressive muscle relaxation. The suggestions given were for hypnotic analgesia, hypnotic anesthesia, and anxiety reduction and varied between patients. The control group received verbal support and attention from the therapist. The primary outcome measure was the amount of pain medication requested and received in a 24-h period. Patients in the hypnosis group received significantly less pain medication than those in the control group ($F = 55.58$, $P < 0.01$ for patients with 31%-60% TBSA; $F = 40.91$, $P < 0.01$ for patients with < 30% TBSA). Patients under 18 used significantly less medication than the adults ($P < 0.05$) which the authors attribute to less psychological resistance. The authors also note that hypnosis may be especially beneficial and highly reinforcing for children who have problems understanding why they are being put through the painful wound cleaning procedures.

An interesting study from Moore *et al*[23] evaluated the efficacy of hypnotically induced vasodilation to aid in healing of burn injuries. A total of 5 patients who had bilaterally symmetrical or comparable burns were enrolled in the study. Only one side of the body was treated through hypnosis, so each patient acted as their own control. The hypnosis included suggestions for increasing blood flow to a certain part of the body, and left or right was clearly specified by the therapist. The patient and the therapist were aware of which side was being treated, but the healthcare staff who evaluated

Table 1 Controlled trials

Ref.	Outcome and measurement method	Intervention	*n*	Randomization	Hypnotizability considered	Control condition	Age range	Significant results
Wakeman *et al*[22] (1978)	Pain intensity Medication usage	During procedures + sessions to teach self-hypnosis Inductions varied between patients (eye-fixation, eye-roll, progressive muscle relaxation) Suggestions for analgesia, anesthesia, and anxiety reduction	42	No	No	Attention	7-70	Less medication with hypnosis (approximately 42.5% less medication overall) Under 18 used less medication than adults
Moore *et al*[23] (1983)	Unilateral healing Skin temperature and observation of inflammation	Suggestions for increased blood flow to injured area	5	No	No	SC on half of body (patient was own control)	Adults	Rapid unilateral healing in 4/5 patients Rapid bilateral healing in 1/5 patients
Margolis *et al*[24] (1983)	Physiological response Fluid input/urine output (fluid retention)	Single early induction Suggestions for coolness and comfort with visual imagery	22	No	Yes (clinical observation)	SC	Adults	No significant between group difference in fluid input Day 2 urine output higher with hypnosis in those judged to be at least mildly hypnotized Percentage urine output higher for hypnosis than control
Hammond *et al*[25] (1983)	Pain VAS Inflammation reduction Temperature and observation of redness	≥ 2 h of hypnotic training by therapist Suggestions for coolness and analgesia on one leg	6	No	Yes (ability to develop glove anesthesia)	No treatment on other leg (patient was own control)	Adults	No pain reported on treated leg Sig trend of lower temperatures on treated leg Lower redness ratings on treated leg
Patterson *et al*[26] (1989)	Pain (dressing change and debridement) VAS	RIA Hypnosis done prior to procedure + nurses providing posthypnotic cues during	13	No	No	Historical	Adults	Lower pain scores with hypnosis
Patterson *et al*[27] (1992)	Pain (during debridement) Medication use VAS (patient-rated, nurse-rated)	RIA on day 2 before procedure Visualize descending a staircase Included posthypnotic suggestions for analgesia cue to be given during procedure	30	Yes	No	Attention (placebo hypnosis), SC	Adults	No sig medication difference between groups Reduction of patient-rated pain with hypnosis Reduction of nurse-rated pain score with hypnosis
Everett *et al*[60] (1993)	Pain (during debridement) VAS (patient-rated, nurse-rated) Medication use	Modified RIA on days 3 and 4 before debridement Included posthypnotic suggestions for cool numbness cue to be given during debridement	32	Yes	No	Attention, Ativan	Adults	No sig pain difference between groups No sig medication difference between groups
Patterson *et al*[28] (1997)	Pain (during debridement) VAS (patient-rated, nurse-rated) Opioid intake	Modified RIA on day 4 before debridement Included posthypnotic suggestions for cool numbness cue to be given during debridement	61	Yes	No	Attention	Adults	No sig pain difference between groups Less pain with hypnosis with high baseline pain Nurses rated less pain with hypnosis No sig medication difference between groups

Wright *et al*[29] (2000)	Pain (dressing change and debridement) Medication usage Pain intensity NRS Pain distress NRS Relaxation	Modified RIA during wound care	30	Yes	No	SC	16-48	Less medication use with hypnosis Reduced pain intensity and distress with hypnosis after first hypnosis session Increased relaxation with hypnosis after wound care
Harandi *et al*[30] (2004)	Pain VAS Procedural anxiety VAS	Modified RIA for ⩾ 2 d	44	No	Yes (Davis-Husband scale)	SC	16-75	Reduction of pain and anxiety with hypnosis N of sessions correlated with lower pain and anxiety
Askay *et al*[31] (2007)	Pain (during debridement) McGill Pain Questionnaire -Short Form	Modified RIA Audio-recorded	46	Yes	Yes (SHCS)	Attention	Adults	Lower McGill pain score with hypnosis
Shakibaei *et al*[32] (2008)	Pain and re-experiencing of trauma Pain NRS Number of patients' recollections of vivid, troubling events the day before	Hypnosis done outside of procedures (to focus on background pain) Eye fixation induction for adults Doll or teddy bears used in induction for children Guided imagery of a cold bath and pain dissipating Posthypnotic suggestions for analgesia and improved sleep	44	Yes	No	SC	6-62	Lower pain ratings with hypnosis compared to control Pain reduction from baseline to 5th session Reduction in re-experiencing scores with hypnosis from baseline to 3rd session and baseline to 5th session
Berger *et al*[33] (2010)	Pain VAS Anxiety ESAS for anxiety Opioid usage Patient charts Economical costs Analytic accounting system	Hypnosis delivered by trained nurse during wound care Induction and suggestions varied according to observation of patient's behavior	23	No	No	Historical	adults	Pain reduction with hypnosis Anxiety reduction with hypnosis Mean opioid doses lower with hypnosis Net savings of €174640

Sig: Significant; SC: Standard care; SHCS: Stanford hypnotic clinical scale; VAS: Visual analogue scale; NRS: Numeric rating scale; RIA: Rapid induction analgesia[59]; ESAS: Edmonton symptom assessment scale.

the healing was kept blind to the treatment. Of the five patients, four exhibited enhanced healing on the treated side as compared to the untreated side. The fifth patient healed faster than expected bilaterally.

Margolis *et al*[24] sought to assess whether or not hypnosis could alter patients' physiological response to their burn wounds. The primary outcome measure was fluid input and urine output. This measure of physiological response was chosen because output of urine is associated with fluid retention or edema. Only one hypnotic induction was given within 12 h of original tissue damage. The hypnosis included suggestions for coolness and comfort with visual imagery. Twenty-two patients completed the study. Eleven of those were in the hypnosis group and the other half were matched controls. Roughly half of the patients were described as being at least mildly hypnotized during the induction. Significant differences between the treatment and control groups were not found for length of hospital stay and fluid intake. Urine output on the second day of the study was found to be significantly higher for the hypnotized patients than for their matched controls (t = 5.43, P < 0.01) with urine output as a percentage of fluid intake being 65.3% for those in the treatment group and 29.8% for the control groups. Overall percentage urine output was also significantly higher for treatment than control group (t = 4.15, P < 0.01). The results suggest that hypnosis affected participants' physiological responses to injury, though more research is needed to assess the mechanisms and possible physiological changes that can occur.

In order to assess hypnotic analgesia and the effectiveness of suggestions for coolness, six participants with bilateral thigh sunburns underwent hypnosis treatment for only one thigh, similar to the Moore *et al*[23] study mentioned above[25]. To ensure that the patients were able to be hypnotized at a high level, they were screened prior to the study to confirm that they were able to achieve glove analgesia and make finger signals to communicate with the therapist. No pain was reported for the area treated from any of the participants. Mean differences of redness and

temperature differences were not statistically significant, though they were consistently lower for the treated side than the control side. The statistically significant findings were the proportion of lower temperatures on the treated thigh compared to the control ($P < 0.01$) and the proportion of redness ratings that were lower for the analgesic side compared to control ($P < 0.01$). Though the sample size was small, researchers concluded that hypnosis may be effective in reducing inflammation from burns.

In a non-randomized study, patients who self-reported high levels of baseline pain received hypnosis for pain before their wound care procedure or were assigned to a standard care control group[26]. For the hypnosis group, researchers used a slightly modified version of Barber's[59] RIA technique, with added suggestions for comfort and numbness. Hypnosis intervention did not start until patients were on a pain medication regimen. A therapist would guide the patient in hypnosis before a cleaning or debridement. The suggestions would include a posthypnotic analgesia cue to be provided during the procedure. Then, a nurse would be given instruction card on how to provide the cue for pain relief, which was a touch on the shoulder. Compared to those in a control condition, those who had received the hypnotic analgesia had a significant drop in pain scores after treatment ($r = 0.94$, $t = 4.76$, $P < 0.025$).

A randomized controlled trial that followed the above study, included 30 adult patients in a hospital[27]. All patients rated their pain as 5 or higher on a 10-point numeric rating scale at baseline. Each patient was randomized into one of three groups: Hypnosis intervention, attention and information control group, or a standard treatment control group. Patients in the active control group (attention and information) were led to believe that what they were experiencing was hypnosis as well. The treatment and active control condition both took place during debridement and the hypnotic induction was again based on Barber's[59] RIA technique. Patients in all three groups still received opioid medications during debridement. Compared to baseline data, scores on a 10 cm visual analogue scale (VAS) were significantly [($t(27) = 4.48$, $P = 0.0001$] lower for the hypnosis group, with a mean pre-treatment to post-treatment difference of 3.8. The scores lowered a non-significant 1.3 and 1.1 for the attention placebo group and the no treatment control group respectively. Corroborating these findings, nurse ratings of patients' pre-treatment to post-treatment pain were significantly decreased for only the treatment group [$t(24) = 3.52$, $P = 0.002$].

In a study also using a burn-specific version of Barber's[59] RIA, researchers studied a sample of burn patients who reported lower baseline pain scores[60]. Patients were randomized into an attention control group or a hypnosis group which included suggestions for pain relief, comfort, and relaxation during wound care. No significant differences in pain or medication usage were found between the hypnosis group, the control and a group in an additional study who received Lorazepam as treatment. The authors concluded that the lack of significance may be because the baseline pain scores were not high enough for the treatment to be especially beneficial.

Supplementing the aforementioned study, Patterson *et al*[28] randomized 61 adult patients to either a hypnosis group or an attention and instruction control group during debridement. When considering only patients whose pain score was above the midpoint on a 10 cm VAS during baseline, significant differences are seen between patients in the hypnosis group and the control group [$F(1,33) = 4.33$, $P < 0.05$]. This was not the case for those that began on the lower end of the VAS. This self-report data suggests that hypnosis may be more beneficial for patients who are experiencing a higher level of baseline pain, similar to the findings of the aforementioned study. However, using the same RIA technique[59] as Patterson *et al*[28], Wright *et al*[29] did find a significant reduction in pain scores irrespective of baseline pain scores [$F(2,23) = 11.18$, $P < 0.01$).

In another randomized controlled trial examining pain as well as treatment anxiety, 44 women were allocated to get either 4 daily hypnotherapy sessions or standard care[30]. This study also used a version of RIA that was modified for burn-pain and included direct suggestions for analgesia. The depth of hypnosis for each patient was measured using the Davis-Husband scale[61]. Using a 10 cm VAS, researchers found that participants receiving hypnotherapy had reported significantly less acute pain ($P < 0.0001$) and procedural anxiety ($P < 0.0001$) than those in the control group. Some patients received additional hypnosis sessions, and the number of sessions significantly correlated with a decrease in pain ($r = -0.55$, $P < 0.0001$) and anxiety ($r = -0.66$, $P < 0.0001$).

Askay *et al*[31] had 46 adult patients randomized to either a hypnosis group or an attention and relaxing music group. Researchers assessed pain using the Short Form McGill Pain Questionnaire (MPQ). Again using a burn treatment specific version of RIA, researchers made recordings of hypnotic inductions to be played during burn care procedures. Significantly larger pain reductions were observed in those in the hypnosis group than in the attention and relaxation group ($P = 0.008$, $d = 0.83$). The decrease in pain was seen when measured by the MPQ, but not other rating scales. This discrepancy led researchers to conclude that the MPQ total score may account for multiple components of pain as opposed to pain intensity alone. Patient hypnotizability was measured using the Stanford Hypnotic Clinical Scale (SHCS)[62], and no significant main effects were found between hypnotizability and outcome.

In a study that focused on both pain care and reducing the re-experiencing of trauma, 44 hospitalized patients were randomized to a hypnotherapy group or a control group[32]. A five-point numeric rating scale was used to assess pain. Trauma re-experiencing was assessed by asking patients daily to list vivid,

disturbing events from their day. The group receiving the experimental treatment had pain scores that were significantly lower than their baseline scores and the control group's endpoint scores ($P < 0.05$). When comparing the pain scores from the baseline measurement to the pain scores after the 5th hypnosis session, there was a significant reduction in pain for the treatment group only ($P < 0.001$). The hypnosis group also demonstrated a significantly lower trauma re-experiencing score ($P < 0.05$), yet there was no significant difference for the control group.

In a recent study of hypnosis for burns, 23 adult patients in an intensive care unit were matched with 23 historical controls[33]. In addition to standard pain care, those who received the experimental treatment underwent hypnosis for pain during wound care procedures roughly a week after their original injury. Measurements taken included an average of daily scores on a VAS for pain and amount of opioid medications used. Anxiety and economical costs were evaluated as well. Within the intervention group, patients had significantly lower pain scores (from 2.5 ± 2.6 to 0.9 ± 1.4 on a VAS, $P < 0.0001$) as well as lower medication usage (first 10 d: $P < 0.0001$; after 15th day: $P = 0.001$). Significantly lower anxiety (from 3.2 ± 2.9 to 1.2 ± 1.7, $P < 0.0001$), less anesthesia, and lower hospital bills were also noted for the patients in the treatment group.

In almost all of the studies, adding hypnosis to standard care aids in reducing pain intensity as well as anxiety or distress. Results for lowering the use of opioids and other pain medications are not as strong, but do generally show a benefit of adjunctive hypnosis.

MECHANISMS FOR HYPNOTIC ANALGESIA

Research of hypnosis and activity in the central nervous system show a glimpse of probable neurological mechanisms of pain control[63]. The existing research involving neuroimaging of hypnoanalgesic effects suggests that hypnosis modulates both cortical and subcortical neural activity to alter awareness and sensitivity to painful sensations[44,64]. Hypnosis may be able to at least partially prevent painful stimuli from reaching neural regions associated with the perception of pain. With hypnotic induction, in painful conditions, there is less activation at the sensory cortex, precuneus, and cingulate gyrus, suggesting that the sensation of pain is dulled[44,65].

In a recent article written to pinpoint neural activation and deactivation patterns in pain conditions curbed by hypnosis, when hypnotic pain relief suggestions were given, deactivation was noted in networks associated with pain sensations, as well as other regions. In these hypnoanalgesia studies, regulations of the anterior cingulate cortex (ACC) through hypnotic suggestions appeared to modify nociception awareness and alter connections between the ACC and other brain regions involved in pain perception such as, the prefrontal, somatosensory, and insular cortices[44,66]. These neuroimaging studies of hypnoanalgesia corroborate the multidimensional quality of hypnoanalgesia and give evidence of the interactions of cortical and subcortical neural structures[44,64,65]. Overall, neuroimaging research substantiates clinical opinions that the use of clinical hypnosis to manage pain conditions is beneficial[44]. There is evidence to support the perception of pain decreasing even without suggestions related to analgesia. This is attributed to the directing of attention away from painful sensory information[66,67], though it is unlikely that the analgesic effects of hypnosis are due solely to distraction[68]. It is generally accepted that the use of specific pain relief suggestions following a hypnotic induction promotes a higher likelihood of success.

A likely mechanism of action is that suggestions may compel patients to implement cognitive skills or strategies to comply with the suggested idea[39,69]. Some studies also suggest that the top-down nature of hypnosis alters the conscious perception of painful stimulation[65,67]. Dissociation theories also offer ideas about the mechanisms of hypnotic analgesia. Research by Rainville *et al*[70,71] suggests that hypnotically suggested dissociation of pain intensity and pain affect can result in a patient who may still feel pain, but is not bothered by it. Long before this theory gained popularity, Bernstein[51] noted that for some patients, hypnosis did not produce anesthesia but did increase pain tolerance.

In regard to mechanisms underlying the effects of hypnosis for burn care in particular, researchers postulated that factors playing a role in how hypnosis impacts pain include motivation to avoid pain, natural trust in health care providers, and dissociation from the stress related to burn wound care[72].

HYPNOTIZABILITY

Most individuals are able to respond to hypnotic suggestions to at least a moderate level[39]. Hypnotizability refers to "an individual's ability to experience suggested alterations in physiology, sensations, emotions, thoughts, or behavior during hypnosis[36]". Standardized scales are available to assess the level to which suggestions will be successful[39,73,74]. Hypnotizability scales are an important tool for practitioners who want to use hypnosis as a treatment or a treatment supplement. Even though most patients seem to be able to benefit from hypnotherapy in a clinical setting, being able to assess a patient or participant's ability to experience suggestions is crucial to treatment design. Hypnotizability testing may hold valuable information on what suggestions may be successful during hypnotic treatment. This information may inform clinicians and researchers alike when implementing hypnotherapy, and can be used to give a better estimation of the treatment effect[39,75-77]. Most professionals in the field agree that there is usefulness

to assessing hypnotic responsiveness and individual differences in hypnotizability are possible to measure[76].

There is a recent push to remove the negative connotation that has been associated with hypnosis through its mysterious nature and use for entertainment purposes. Earlier hypnotizability scales used the word "susceptibility" to describe the depth of dissociation an individual could achieve[75]. Newer scales use the words "hypnotizability" or "hypnotic talents" to highlight the positive aspects of being able to respond well to hypnotic treatment[39]. Additionally, the term "hypnotic relaxation therapy" has been introduced to indicate the use of evidence-based hypnosis in medical and psychological practice[39]. This is in line with an overall drive to guide hypnosis to a more empirically-based connotation.

As evidenced by the current literature, hypnotizability is rarely measured in burn pain studies. When it is measured, results indicate little to no correlation with the treatment effect. A meta-analysis found a small, yet significant, association between hypnotizability and outcomes in various clinical contexts[78]. The level of hypnotizability accounted for only 6% of the outcome variance, which suggests that the success of an intervention will likely not depend on the individual's hypnotizability. Hypnosis is likely still a valuable treatment option for acute cases, in which care is needed immediately and there is no time to measure hypnotizability[57,78]. Though there is little evidence that hypnotizability would be an imperative aspect of integrating hypnosis into a treatment plan for burn patients, measuring a patient's hypnotizability may have additional benefits when time allows. For instance, hypnotizability scales allow for the establishment of correct expectancies and introduce hypnosis to a patient who may be mildly skeptical. Also, discussing the scale and the patient's results provides a setting for planning the course of treatment. For instance, those who fall lower on the hypnotizability spectrum may need one or more introductory session or further personalization to ensure the best results[39].

LIMITATIONS AND FUTURE RESEARCH

Though the results of using hypnosis in burn treatments can often be remarkable, over-expectation should be avoided. Generally, hypnosis is not the sole anesthetic used in major surgeries, but an adjunct to a lower dose of chemical anesthetics. The effectiveness of hypnotic analgesia should be tested prior to surgeries or procedures. Conditioning or training the patient should also be done prior to wound care so they know what to expect and any complaints of pain can be noted before a surgery is underway. If the patient complains of pain or seems to prematurely return to alertness, supplementary conditioning sessions can be used. Even with successful prior conditioning and testing, the anesthesiologists should be prepared to employee additional chemical agents if needed[48].

Patients should also be made aware of what will occur during medical procedures in order to avoid surprises that may disturb their experience of hypnosis. Some hypnotic inductions used during procedures may only include suggestions aimed at a certain region of the body, and a touch in an unexpected area could lead to an abrupt response. If they are delivering hypnosis during a procedure, therapists should be prepared to tailor suggestions to the situation in case something unexpected happens[48].

When using hypnosis during a procedure, healthcare personnel should note that the patient may be more aware of what is said in the room than a patient under only chemical anesthesia. The therapist using hypnosis may want to suggest that the patient hear only the voice of the therapist and to not be distracted by other sounds in the room. However, any remark that would be inappropriate or upsetting to a patient who was fully conscious should still be avoided[48].

The results from the studies mentioned here suggest that hypnosis is a valuable tool for healthcare providers who treat burned patients. However, it is also clear from the review of research that more comprehensive randomized controlled trials are need. For instance, many of the studies did not take the hypnotizability of the patients into account. Future studies should assess whether the benefits of integrating hypnosis into standard burn care is meaningful even for those who are on the low end of the hypnotizability spectrum. There was also mixed evidence for the extent of benefit that hypnosis treatment may have on patients who have a relatively low baseline pain. Future research could assess whether patients with a low baseline pain feel that the changes they experience with adjunct hypnosis is meaningful to them or whether factors besides pain are affected. The current literature is also lacking research on chronic pain for those on the long course to burn recovery. New studies that consider the full range of pain stages are needed.

Vital to maximizing the safety and effectiveness of burn care is instituting a multidisciplinary burn team that includes someone trained to care for the psychological needs of each patient. In a recent chapter, Alter[79] explains the levels of certification in clinical hypnosis including paths to accreditation, consultant, board certification, and continuing education credits. In the United States, certification programs in clinical hypnosis are available through the American Society of Clinical Hypnosis (ASCH) and the Society for Clinical and Experimental Hypnosis (SCEH). Other countries may require alternate licensure. Certification is reserved for those who have an advanced degree in a field related to psychology, counseling, social work or medicine[79].

CONCLUSION

Burn wound aftercare is inherently agonizing and stressful. Therefore, it follows that a therapy aimed at relaxing the patient and allowing them to feel more empowered in their treatment would be helpful. Attending

to not only the physical needs, but also the psychological needs of each patient leads to improvements beyond the standard pain relief. Due to possible complications from the use of opioids or other medications, a non-pharmacological treatment is needed as a complement to conventional treatment. Multimodal burn treatments allow a calmer environment and less pain for patients while possibly cutting the amount of drugs that are needed. Research shows that hypnosis can accomplish more than simply relaxing the patient temporarily. Hypnosis can have effects beyond the treatment room and, occasionally, beyond the patients' expectations. While more rigorous experimental research is needed to further our knowledge of the mechanisms with which clinical hypnosis benefits patients and what the optimal "dose" is, this powerful tool should not be overlooked by practitioners. Advancing this research is key to furthering the understanding of hypnosis and how it can most efficiently be used to help those who are suffering from burn-related pain.

REFERENCES

1 **Patterson DR**, Hofland HW, Espey K, Sharar S. Pain management. *Burns* 2004; **30**: A10-A15 [PMID: 15555783 DOI: 10.1016/j.burns.2004.08.004]

2 **Sharar SR**, Miller W, Teeley A, Soltani M, Hoffman HG, Jensen MP, Patterson DR. Applications of virtual reality for pain management in burn-injured patients. *Expert Rev Neurother* 2008; **8**: 1667-1674 [PMID: 18986237 DOI: 10.1586/14737175.8.11.1667]

3 **McRobert J**. The psychosocial impact on patients with altered body image from burns. *Br J Commun Nurs* 2012; **17**: 27-30

4 **Menzies V**. Depression and burn wounds. *Arch Psychiatr Nurs* 2000; **14**: 199-206 [PMID: 10969640 DOI: 10.1053/apnu.2000.8660]

5 **Morten K**. Personality characteristics and perceived health problems after burn injury. *J Burn Care Rehabil* 2004; **25**: 228-235

6 **van Twillert B**, Bremer M, Faber AW. Computer-generated virtual reality to control pain and anxiety in pediatric and adult burn patients during wound dressing changes. *J Burn Care Res* 2007; **28**: 694-702 [PMID: 17667488 DOI: 10.1097/BCR.0B013E318148C96F]

7 **Pedersen JL**, Kehlet H. Hyperalgesia in a human model of acute inflammatory pain: a methodological study. *Pain* 1998; **74**: 139-151 [PMID: 9520228]

8 **Richardson P**, Mustard L. The management of pain in the burns unit. *Burns* 2009; **35**: 921-936 [PMID: 19505764 DOI: 10.1016/j.burns.20007.03.003]

9 **Wilder-Smith OH**, Arendt-Nielsen L. Postoperative hyperalgesia: its clinical importance and relevance. *Anesthesiology* 2006; **104**: 601-607 [PMID: 16508408]

10 **Patterson DR**, Sharar S. Burn Pain. In Loeser J, editor. Bonica's management of pain. 3rd ed., Phidelphia, PA: Lippincot, Williams & Wilkins; 2001: 780-787

11 **Loncar Z**, Bras M, Micković V. The relationships between burn pain, anxiety and depression. *Coll Antropol* 2006; **30**: 319-325 [PMID: 16848146]

12 **Edwards RR**, Smith MT, Klick B, Magyar-Russell G, Haythornthwaite JA, Holavanahalli R, Patterson DR, Blakeney P, Lezotte D, McKibben J, Fauerbach JA. Symptoms of depression and anxiety as unique predictors of pain-related outcomes following burn injury. *Ann Behav Med* 2007; **34**: 313-322 [PMID: 18020941 DOI: 10.1080/08836610701677725]

13 **Summer GJ**, Puntillo KA, Miaskowski C, Green PG, Levine JD. Burn injury pain: the continuing challenge. *J Pain* 2007; **8**: 533-548 [PMID: 17434800 DOI: 10.1016/j.jpain.2007.02.426]

14 **Taal LA**, Faber AW. Burn injuries, pain and distress: exploring the role of stress symptomatology. *Burns* 1997; **23**: 288-290 [PMID: 9248635]

15 **Kehlet H**. Surgical stress: the role of pain and analgesia. *Br J Anaesth* 1989; **63**: 189-195 [PMID: 2669908]

16 **Page GG**. The medical necessity of adequate pain management. In: Pain Forum (Churchill Livingstone) 1997; **5**: 227-233

17 **Picard P**, Jusseaume C, Boutet M, Dualé C, Mulliez A, Aublet-Cuvellier B. Hypnosis for management of fibromyalgia. *Int J Clin Exp Hypn* 2013; **61**: 111-123 [PMID: 23153388 DOI: 10.1080/00207144.2013.729441]

18 **Patterson DR**, Wiechman SA, Jensen M, Sharar SR. Hypnosis delivered through immersive virtual reality for burn pain: A clinical case series. *Int J Clin Exp Hypn* 2006; **54**: 130-142 [PMID: 16581687 DOI: 10.1080/00207140500528182]

19 **Fernandez E**, Turk DC. The utility of cognitive coping strategies for altering pain perception: a meta-analysis. *Pain* 1989; **38**: 123-135 [PMID: 2674861]

20 **Palermo TM**, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. *Pain* 2010; **148**: 387-397 [PMID: 19910118 DOI: 10.1016/j.pain.2009.10.004]

21 **Williams AC**, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2012; **11**: CD007407 [PMID: 23152245 DOI: 10.1002/14651858.CD007407.pub3]

22 **Wakeman JR**, Kaplan JZ. An experimental study of hypnosis in painful burns. *Am J Clin Hypn* 1978; **21**: 3-12 [PMID: 696661 DOI: 10.1080/00029157.1978.10403952]

23 **Moore LE**, Kaplan JZ. Hypnotically accelerated burn wound healing. *Am J Clin Hypn* 1983; **26**: 16-19 [PMID: 6678106 DOI: 10.1080/00029157.1983.10404132]

24 **Margolis CG**, Domangue BB, Ehleben C, Shrier L. Hypnosis in the early treatment of burns: a pilot study. *Am J Clin Hypn* 1983; **26**: 9-15 [PMID: 6678116 DOI: 10.1080/00029157.1983.10404131]

25 **Hammond DC**, Keye WR, Grant CW. Hypnotic analgesia with burns: an initial study. *Am J Clin Hypn* 1983; **26**: 56-59 [PMID: 6678115 DOI: 10.1080/00029157.1983.10404140]

26 **Patterson DR**, Questad KA, de Lateur BJ. Hypnotherapy as an adjunct to narcotic analgesia for the treatment of pain for burn debridement. *Am J Clin Hypn* 1989; **31**: 156-163 [PMID: 2563925 DOI: 10.1080/00029157.1989.10402884]

27 **Patterson DR**, Everett JJ, Burns GL, Marvin JA. Hypnosis for the treatment of burn pain. *J Consult Clin Psychol* 1992; **60**: 713-717 [PMID: 1383302]

28 **Patterson DR**, Ptacek JT. Baseline pain as a moderator of hypnotic analgesia for burn injury treatment. *J Consult Clin Psychol* 1997; **65**: 60-67 [PMID: 9103735]

29 **Wright BR**, Drummond PD. Rapid induction analgesia for the alleviation of procedural pain during burn care. *Burns* 2000; **26**: 275-282 [PMID: 10741595]

30 **Harandi A**, Esfandani A, Shakibaei F. The effect of hypnotherapy on procedural pain and state anxiety related to physiotherapy in women hospitalized in a burn unit. *Contemp Hypn* 2004; **21**: 28-34 [DOI: 10.1002/ch.285]

31 **Askay S**, Patterson D, Jensen M, Sharar S. A randomized controlled trial of hypnosis for burn wound care. *Rehabil Psychol* 2007; **52**: 247-253 [DOI: 10.1037/0090-5550.52.3.247]

32 **Shakibaei F**, Harandi AA, Gholamrezaei A, Samoei R, Salehi P. Hypnotherapy in management of pain and reexperiencing of trauma in burn patients. *Int J Clin Exp Hypn* 2008; **56**: 185-197 [PMID: 18307128 DOI: 10.1080/00207140701849536]

33 **Berger MM**, Davadant M, Marin C, Wasserfallen J, Pinget C, Maravic P, Koch N, Raffoul W, Chiolero R. Impact of a pain protocol including hypnosis in major burns. *Burns* 2010; **36**: 639-646 [DOI: 10.1016/j.burns.2009.08.009]

34 **Mock C**, Peck M, Peden M, Krug E, eds. A WHO plan for burn prevention and care. Geneva: World Health Organization, 2008

35 **Stoelb BL**, Molton IR, Jensen MP, Patterson DR. The efficacy of hypnotic analgesia in adults: a review of the literature. *Contemp*

Hypn 2009; **26**: 24-39 [PMID: 20161034 DOI: 10.1002/ch.370]
36 **Elkins GR**, Barabasz AF, Council JR, Spiegel D. Advancing Research and Practice: The Revised APA Division 30 Definition of Hypnosis. *Am J Clin Hypn* 2015; **57**: 378-385 [PMID: 25928776 DOI: 10.1080/00029157.2015.1011465]
37 **Kirsh I**, Lynn S. Dissociation theories of hypnosis. *Psych Bul* 1998; **123**: 100 [DOI: 10.1037/0033-2909.123.1.100]
38 **Kekecs Z**, Nagy T, Varga K. The effectiveness of suggestive techniques in reducing postoperative side effects: a meta-analysis of randomized controlled trials. *Anesth Analg* 2014; **119**: 1407-1419 [PMID: 25289661 DOI: 10.1213/ANE.0000000000000466]
39 **Elkins G**. Hypnotic relaxation therapy: Principles and applications. New York, NY: Springer Publishing Company, 2014
40 **Elkins G**. Handbook of medical and psychological hypnosis: Foundations, applications, and professional issues. New York, NY: Springer Publishing Company, 2017
41 **Elkins G**, Johnson A, Fisher W. Cognitive hypnotherapy for pain management. *Am J Clin Hypn* 2012; **54**: 294-310 [PMID: 22655332 DOI: 10.1080/00029157.2011.654284]
42 **Wolsko PM**, Eisenberg DM, Davis RB, Phillips RS. Use of mind-body medical therapies. *J Gen Intern Med* 2004; **19**: 43-50 [PMID: 14748859 DOI: 10.1111/j.1525-1497.2004.21019.x]
43 **Adachi T**, Fujino H, Nakae A, Mashimo T, Sasaki J. A meta-analysis of hypnosis for chronic pain problems: a comparison between hypnosis, standard care, and other psychological interventions. *Int J Clin Exp Hypn* 2014; **62**: 1-28 [PMID: 24256477 DOI: 10.1080/00207144.2013.841471]
44 **Del Casale A**, Ferracuti S, Rapinesi C, Serata D, Caltagirone SS, Savoja V, Piacentino D, Callovini G, Manfredi G, Sani G, Kotzalidis GD, Girardi P. Pain perception and hypnosis: findings from recent functional neuroimaging studies. *Int J Clin Exp Hypn* 2015; **63**: 144-170 [PMID: 25719519 DOI: 10.1080/00207144.2015.1002371]
45 **Elkins G**, Jensen MP, Patterson DR. Hypnotherapy for the management of chronic pain. *Int J Clin Exp Hypn* 2007; **55**: 275-287 [PMID: 17558718 DOI: 10.1080/00207140701338621]
46 **Kendrick C**, Sliwinski J, Yu Y, Johnson A, Fisher W, Kekecs Z, Elkins G. Hypnosis for Acute Procedural Pain: A Critical Review. *Int J Clin Exp Hypn* 2016; **64**: 75-115 [PMID: 26599994 DOI: 10.1080/00207144.2015.1099405]
47 **Lang EV**, Rosen MP. Cost analysis of adjunct hypnosis with sedation during outpatient interventional radiologic procedures. *Radiology* 2002; **222**: 375-382 [PMID: 11818602 DOI: 10.1148/radiol.2222010528]
48 **Crasilneck HB**, Hall JA. Clinical hypnosis: Principles and applications. Orlando, FL: Grune & Stratton, 1985
49 **Crasilneck HB**, Jenkins MT, Mccranie EJ. Special indications for hypnosis as a method of anesthesia. *J Am Med Assoc* 1956; **162**: 1606-1608 [PMID: 13376327]
50 **Crasilneck HB**, Stirman JA, Wilson BJ, Mccranie EJ, Fogelman MJ. Use of hypnosis in the management of patients with burns. *J Am Med Assoc* 1955; **158**: 103-106 [PMID: 14367047]
51 **Bernstein NR**. Management of burned children with the aid of hypnosis. *J Child Psychol Psychiatry* 1963; **4**: 93-98 [PMID: 14055466]
52 **Bernstein NR**. Observations on the use of hypnosis with burned children on a pediatric ward. *Int J Clin Exp Hypn* 1965; **13**: 1-10 [PMID: 14255620 DOI: 10.1080/00207146508412920]
53 **Ewin DM**. Emergency room hypnosis for the burned patient. *Am J Clin Hypn* 1983; **26**: 5-8 [PMID: 6678113 DOI: 10.1080/00029157.1983.10404130]
54 **Ewin DM**. Hypnosis in surgery and anesthesia. In: Wester WC, Smith A, eds. Clinical hypnosis: A multidisciplinary approach. Philidelphia, PA: Lippincott, 1984
55 **Ewin DM**. Emergency room hypnosis for the burned patient. *Am J Clin Hypn* 1986; **29**: 7-12 [PMID: 3739965 DOI: 10.1080/00029157.1986.10402672]
56 **Ewin DM**. Clinical use of hypnosis for attenuation of burn depth. In: Hypnosis at its Bicentennial. US : Springer, 1978: 155-162
57 **Manusov EG**, Murray G. Acute trauma and hypnosis. *Mil Med* 1992; **157**: 504-505 [PMID: 1454201]
58 **Ohrbach R**, Patterson DR, Carrougher G, Gibran N. Hypnosis after an adverse response to opioids in an ICU burn patient. *Clin J Pain* 1998; **14**: 167-175 [PMID: 9647460]
59 **Barber J**. Rapid induction analgesia: a clinical report. *Am J Clin Hypn* 1977; **19**: 138-145 [PMID: 835486 DOI: 10.1080/00029157.1977.10403860]
60 **Everett JJ**, Patterson DR, Burns GL, Montgomery B, Heimbach D. Adjunctive interventions for burn pain control: comparison of hypnosis and ativan: the 1993 Clinical Research Award. *J Burn Care Rehabil* 1993; **14**: 676-683 [PMID: 7507933]
61 **Davis LW**, Husband RW. A study of hypnotic susceptibility in relation to personality traits. *J Abnorm Soc Psych* 1931; **26**: 175–82 [DOI: 10.1037/h0074985]
62 **Hilgard ER**, Hilgard JR. Hypnosis in the relief of pain. Los Altos, CA: Kaufmann, 1975
63 **Patterson DR**, Jensen MP. Hypnosis and clinical pain. *Psychol Bull* 2003; **129**: 495-521 [PMID: 12848218 DOI: 10.1037/0033-2909.129.4.495]
64 **Wik G**, Fischer H, Bragée B, Finer B, Fredrikson M. Functional anatomy of hypnotic analgesia: a PET study of patients with fibromyalgia. *Eur J Pain* 1999; **3**: 7-12 [PMID: 10700332 DOI: 10.1053/eujp.1998.0093]
65 **Schulz-Stübner S**, Krings T, Meister IG, Rex S, Thron A, Rossaint R. Clinical hypnosis modulates functional magnetic resonance imaging signal intensities and pain perception in a thermal stimulation paradigm. *Reg Anesth Pain Med* 2004; **29**: 549-556 [PMID: 15635514]
66 **Faymonville ME**, Roediger L, Del Fiore G, Delgueldre C, Phillips C, Lamy M, Luxen A, Maquet P, Laureys S. Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis. *Brain Res Cogn Brain Res* 2003; **17**: 255-262 [PMID: 12880897 DOI: 10.1016/S0926-6410(03)00113-7]
67 **Vanhaudenhuyse A**, Boly M, Balteau E, Schnakers C, Moonen G, Luxen A, Lamy M, Degueldre C, Brichant JF, Maquet P, Laureys S, Faymonville ME. Pain and non-pain processing during hypnosis: a thulium-YAG event-related fMRI study. *Neuroimage* 2009; **47**: 1047-1054 [PMID: 19460446 DOI: 10.1016/j.neuroimage.2009.05.031]
68 **Faymonville ME**, Boly M, Laureys S. Functional neuroanatomy of the hypnotic state. *J Physiol Paris* 2006; **99**: 463-469 [PMID: 16750615 DOI: 10.1016/j.jphysparis.2006.03.018]
69 **Nash MR**, Barnier AJ. The Oxford handbook of hypnosis: Theory, research, and practice. Oxford, UK: Oxford University Press, 2008
70 **Rainville P**, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997; **277**: 968-971 [PMID: 9252330]
71 **Rainville P**, Carrier B, Hofbauer RK, Bushnell MC, Duncan GH. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain* 1999; **82**: 159-171 [PMID: 10467921]
72 **Patterson DR**, Adcock RJ, Bombardier CH. Factors predicting hypnotic analgesia in clinical burn pain. *Int J Clin Exp Hypn* 1997; **45**: 377-395 [PMID: 9308266 DOI: 10.1080/00207149708416139]
73 **Barber TX**, Wilson SC. The Barber Suggestibility Scale and the Creative Imagination Scale: experimental and clinical applications. *Am J Clin Hypn* 1978; **21**: 84-108 [PMID: 747170 DOI: 10.1080/00029157.1978.10403966]
74 **Weitzenhoffer AM**, Hilgard ER. Stanford hypnotic susceptibility scale, form C. Palo Alto, CA: Consulting Psychologists Press, 1962
75 **Hilgard ER**. The Stanford Hypnotic Susceptibility Scales as related to other measures of hypnotic responsiveness. *Am J Clin Hypn* 1978; **21**: 68-83 [PMID: 747169 DOI: 10.1080/00029157.1978.10403965]
76 **Lynn SJ**, Shindler K. The role of hypnotizability assessment in treatment. *Am J Clin Hypn* 2002; **44**: 185-197 [PMID: 11799533 DOI: 10.1080/00029157.2002.10403479]
77 **Frischholz EJ**. Hypnosis, hypnotizability, and placebo. *Am J Clin Hypn* 2015; **57**: 165-174 [PMID: 25928603 DOI: 10.1080/00029157.2015.967088]
78 **Montgomery GH**, Schnur JB, David D. The impact of hypnotic suggestibility in clinical care settings. *Int J Clin Exp Hypn* 2011; **59**: 294-309 [PMID: 21644122 DOI: 10.1080/00207144.2011.570656]

79 **Alter D**. Certification in hypnosis and specialty boards. In: Elkins G, ed. Handbook of medical and psychological hypnosis: Foundations, applications, and professional issues. New York, NY: Springer Publishing Company, 2017

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MINIREVIEWS

Massive transfusion: An update for the anesthesiologist

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Abstract

Exsanguination from trauma, gastrointestinal bleeding, and obstetric hemorrhage remains a major source of mortality across the planet. Continued research into resuscitation strategies and evolving technology and blood product storage has allowed for patient to undergo very large volume transfusions, even to the point of replacing a patient's blood volume several times over. As massive transfusions have become more common, more studies have been performed delineating the exact patient population that would benefit, start- and stop-points of transfusions, complications and avoidance of the same. We discuss these points and provide information and strategies for massive transfusion.

Key words: Massive transfusion protocol; Exsanguinating blood loss; Blood transfusion; Trauma surgery

Core tip: Recognizing the patient who requires massive transfusion early is key to the most optimal outcome. Once recognized, massive transfusion protocols (MTP) should be initiated and continued until normal physiologic parameters are reached and definitive control of bleeding is achieved. Hospitals should develop their own MTP, guided by the literature, and according to their specific needs and patient populations.

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INTRODUCTION

Trauma continues to be a major source of mortality, and much of this early mortality comes from exsanguination leading to death. To combat this, strategies to rapidly and effectively administer blood products and associated

adjuncts to control blood loss as quickly as possible. Most deaths due to blood loss happen in the first 6 h[1]. While definitive control occurs in the operating room or interventional radiology suite, continued resuscitation is necessary to keep the patient alive during the critical first hour of the bleeding patient's arrival to the hospital. The goal of massive transfusion is not just the replacement of intravascular volume, but the correction of trauma induced coagulopathy, in an attempt to curb further blood loss. Massive transfusion, defined as > 10 units of blood in the first 24 h can be a life-saving maneuver for a bleeding patient, but is not without complications[2]. Massive transfusion remains an area of great study throughout the critical care and trauma literature, and many hospitals now have developed their own massive transfusion protocols (MTP). This review will discuss the recent advances in massive transfusion, initiation of MTP, special populations, and complications of MTP.

WHEN TO INITIATE MTP

Initiation of MTP was formerly firmly under clinician gestalt. However, this intuition appears to have only a 50% predictive value in identification of patients who will need MTP[3]. Recently, clinicians developed massive resuscitation scoring systems to accurately identify patients who will ultimately require large volume blood product resuscitation upon arrival to the emergency department.

Early identification of this cohort is important before the tipping point of hemorrhage spirals into the lethal triad of coagulopathy. Cotton *et al*[4] found that both short-term and long-term survival is increased when the initiation of MTP occurs immediately in the emergency room rather than later in the operating room. Implementation of MTP guidelines both decrease mortality and the overall amount of blood use in 24 h, due to better proximal resuscitation[5].

Therefore, scoring systems for initiation of MTP must have appropriate sensitivity and also specificity to safely rule out those who will not require large volumes of blood products thus limiting unnecessary infectious exposure and saving valuable resources. These models vary in their variables of laboratory values, physical exam findings, and physiological triggers, but all have comparable predictive abilities. Application of these scoring systems is dependent on the ability for point of care testing in individual hospitals.

The German originated trauma associated severe hemorrhage score (TASH) was the first massive transfusion scoring system. It has 7 variables involving history (gender), physical findings (FAST, long-bone or pelvic fractures), vital signs (heart rate, blood pressure), and laboratory values (base deficit, hemoglobin)[6]. The probability for MTP = 1[1 + exp(4.9 - 0.3 × TASH)].

The Assessment of Blood Consumption score was designed to be applicable on immediate arrival to the emergency room without additional laboratory testing or need for additional calculations. It assigns one point to: Penetrating mechanism, heart rate > 90 bpm, positive FAST, or SBP < 90 mmHg. An Assessment of Blood Consumption score of greater than 2 was determined to be the appropriate trigger for MTP, with a sensitivity and specificity of 75% and 86%, respectively[7].

Cessation of MTP may more nebulous and reliant on clinician gestalt given the potentially rapidly changing current of the patients' clinical condition in the short hours after admission. Following surgical control of bleeding, the restoration of hemodynamics, correction of acidosis and coagulopathy, and signs of sufficient end-organ perfusion (mental status, urine output) all may be used as surrogates for adequate resuscitation. Callcut *et al*[8] identified those patients at risk of ongoing hemorrhage at 6 h after admission and those patients unlikely to need additional blood products. The authors MTP score is composed of 5 variables (INR > 1.5, hemoglobin < 11 g/dL, base deficit > 6) and vital sign (SBP < 90 mmHg, temperature < 35.5 ℃). Failure of normalization of the MTP score within 3 and 6 h associated with mortality at one day and 28 d.

Compliance to MTP is vitally important, as it has been shown to negatively affect survival. In their institutional review, Bawazeer *et al*[9] found delays in 50% of activation and a 47% incidence of non-compliance with type of product given. The authors found significant differences in mortality between groups of high and medium compliance.

Despite the aforementioned algorithmic calculations for initiation and cessation of MTP, providers will often initiate MTP on the early evidence or concern for significant hemorrhage, *i.e.,* initial thoracic or pelvic radiography showing hemothorax or open book pelvic fracture, respectively. It is our suggestion to place institutional protocols to limit the number of people with the power to activate MTP to prevent overutilization by providers inexperienced with the set activation points.

BLOOD PRODUCT RATIOS

Many early studies in blood product ratios of fresh frozen plasma (FFP) to blood and platelet ratios were affected by survival or selection biases and mixed populations[10-12]. Most studies have focused on the risks and benefits associated with a 1:2 or 1:1 ratios of FFP to blood, although other less common ratios exist[13]. With the findings of the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study group published in 2015, many hospitals have decided on a 1:1:1 ratio of products[14]. The PROPPR group prospectively randomized patients at 12 centers to receive 1:1:1 or 1:2:1. While 30-d mortality was similar, there was an increase in early hemostasis and decrease in deaths due to bleeding, at the expense of increased use of blood products. No increase in transfusion-related complications was noted in the 1:1:1 group[14]. The practical matter of having to thaw plasma results in many hospitals having to "catch up", using blood first, then using plasma once it is thawed. This

is disadvantageous as maintaining clotting factors and fibrinogen is important to achieving early hemostasis. A fibrinogen level lower than < 100 mg/dL substantially increases in-hospital mortality[15]. Alternatives to "catching up" include keeping a small number of units of thawed plasma and rotating it out as necessary, or using lyophilized plasma.

ADJUNCTS TO MASSIVE TRANSFUSION

In addition to a balanced hemostatic resuscitation (BHR) protocol multiple other pharmacologic adjuncts have been studied. Initially utilized for procedural related hemorrhage in hemophilic patients[16], tranexamic acid (TXA) was found to have application in the management of surgical bleeding. Multiple studies demonstrated a role for reduced use of blood products in elective surgery as well as the treatment of hyperfibrinolysis associated with cardiopulmonary bypass[16-19]. TXA is a lysine analog which, similar to aminocaproic acid, inhibits fibrinolysis. The antifibrinolytic effect is attributed to its competitive inhibition of the lysine binding site on plasminogen, resulting in the molecules stability and prevents further degradation of the existing clot[20,21]. In 2010 the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH)-2 study reported the results of a 20000 patient RTC in which the effects of TXA on mortality and transfusion requirements in adult patients who were traumatically injured and in hemorrhagic shock[22]. The CRASH-2 group was able to demonstrate an improvement in all-cause mortality and mortality attributed to hemorrhage with the use of TXA within 3 h from time of injury. Subsequent studies, such as the MATTERs (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation) and PED-TRAX (Pediatric Trauma and Tranexamic Acid), demonstrated a survival advantage when TXA was administered[23,24]. In the MATTERs study there was an observed lower unadjusted mortality rate, increased odds of survival and lower rate of coagulopathy[23]. With PED-TRAX, the first study to look at children independently, there was an observed decreased mortality among all patients (OR = 0.3; P = 0.03) who received TXA[24]. Interestingly both populations of the MATTERs and PED-TRAX studies who received TXA were more severely injured than those who did not yet there remained an observed survival benefit.

Regarding thromboembolic events, there was an observed increase in pulmonary embolus and deep venous thrombosis in the MATTERs study but these results were not replicated in the PED-TRAX study[23,24]. While there appears a clear benefit to use of TXA in the bleeding trauma population, several critiques have arisen specifically regarding the CRASH-2 study. These include the applicability and predictability, lack of measurement of severity of injury and the application of TXA use in traumatic brain injury[25]. Several upcoming studies like CRASH-3 and the Prehospital Antifibrinolytics for Traumatic Coagulopathy and Hemorrhage Trial will hopefully elucidate a more specified role for TXA, but what we do know is that TXA provides some benefit to the bleeding trauma patient, and is included in many transfusion protocols[26,27].

The use of supplemental fibrinogen, Recombinant Factor VII (rFVIIa), and prothrombin complex (PCC) as adjuncts to BHR have also been explored. Several nonrandomized trials have evaluated the use fibrinogen in the trauma patient[28-30]. In each of these studies there was a reduced requirement for blood product transfusion and associated reduced potential for multiorgan failure. While there has been shown a benefit, no prospect randomized trials have been reported to date. rFVIIa has also been examined for use in massive transfusion. Multiple retrospective studies have elevated the added effect of rFVIIa on volume of transfusion, mortality and organ failure with mixed results[31-34]. To date, only two randomized controlled trials have been completed[35,36]. Unfortunately, neither study revealed any mortality benefit with the addition of Factor VII though there was observed reduction in amount of blood products transfused, furthermore a Cochrane review was unable to support the use of Factor VII for use in traumatic hemorrhage[37]. PCC has also been proposed for use in BHR. Initially utilized in the treatment of hemophilia, it is the standard reversal agent for vitamin K antagonists and has been utilized in BHR[38]. Several well-constructed reviews and retrospective studies have shown efficaciousness of PCC in addressing vitamin K antagonistic bleeding in trauma, but no clear role in it use in BHR has been defined[39-41]. Hannon *et al*[42] in an animal based model of traumatic coagulopathy failed to show any benefit on blood volume lost when PCC was utilized and there is currently a lack of prospective randomized controlled trials to guide evidence supported use. Although promising, additional prospective study is needed of concentrated fibrinogen or prothrombin complex concentrate before they can be recommended[43].

While a balanced hemostatic resuscitation is the cornerstone of addressing the bleeding trauma patient, there remains much work to be done in the investigation of the multiple potential and available adjuncts before the optimal strategy is determined.

BLOOD ADMINISTRATION METHODS

Speed of transfusion is important during MTP especially when exsanguination occurs at a rate greater than transfusion. Speed is augmented by optimal vascular access and utilizing Pouiselle's law, which states flow is directly related to width and indirectly related to length of the catheter. Pressurized tubing or specialized pressurized rapid transfusers can augment flow. Rapid transfuser units can often also warm blood at the same time, providing an additional benefit against hypothermia.

Blood and fluid warming is important as to not to exacerbate hypothermia. Barthel *et al*[44] suggest

warmed fluids cannot induce hyperthermia, but can limit additional heat loss. However, adjunctive techniques of warming including forced air devices, blankets, and high operating room temperatures are important. Hypothermia is exceedingly dangerous; in patients undergoing MTP, a cutoff of less than 35 ℃ as the lowest recorded temperature in the first 24 h portended increases in mortality[45].

SPECIAL POPULATIONS

Elderly patients

The elderly patient represents a unique challenge amongst the trauma population at base line. Underlying cardiovascular disease and decreased functional status can complicate resuscitation. Data from the PROMMTT and PROPPR had median ages for 37 and 34 years respectively, which questions the applicability of such practices to an elderly population[14,46]. The Trauma Outcomes Group demonstrated that age is an independent predictor of mortality in the massively transfused patient[2]. In theory the decreased need for crystalloid volume would lead to a decreased incidence of circulatory over load in the elderly population. Although no subgroup analysis of the PROMMTT or PROPPER studies exists and no prospective institutional studies exist to examine age in a massive transfusion protocol. In a retrospective analysis of 14 elderly (> 60 years) compared to 52 non-elderly patients, Murry *et al*[47] demonstrated similar, mortality rates (50% *vs* 53%). This is a limited study with high mortality in both arms, but otherwise similar patient characteristics on arrival including GCS, ISS and starting hematocrits. Mitra *et al*[48] retrospectively compared patients > 65 years *vs* a younger cohort and demonstrated that while mortality was higher (39% elderly *vs* 21% young) a significant number of elderly patients survived to discharge. Patient characteristics that were associated with mortality among the elderly patients included an increased systolic blood pressure (OR = 1.02), a pre hospital GCS < 8 (0.73), and acute traumatic coagulopathy (11.75). Limited data exists for the use of massive transfusions in the elderly trauma patient. Small series would suggest similar mortality to cohorts from the same institutions, further work to explore coagulopathic complications is needed. Additionally, considerations for age, frailty and cardiovascular function should be investigate and possibly included in future targeted massive transfusion protocols.

Pediatric patient

The pediatric patient population also represents unique challenges to hemorrhagic shock and acute traumatic coagulopathy. The physiologic reserve in children is robust and includes the ability to maintain normal blood pressures until 20% of blood volume loss[49]. Which make application standard triggers used in adults difficult to apply. Resuscitation in the pediatric population is defined on volume (mL) per body weight (kg) and is no different in acute hemorrhage. Children younger than 3 mo are estimated to 90 mL/kg of blood volume and those older than 3 mo are estimated at 70 mL/kg[50]. Some measures do apply: High ISS scores, shock, high base deficit and increased INR > 1.5 are associated with increased mortality in the pediatric population[51]. In an effort to better define the volume of blood loss needed to qualify for a pediatric MTP, Neff *et al*[52] used the DOD trauma registry and identified all pediatric patients, those to greater than 40 mL/kg of blood loss in the initial 24 h were more often in shock, hypothermic, coagulopathic and thrombocytopenic at time of presentation[52,53]. This gives a reasonable initial starting point for a volume trigger for pediatric MTP. The same principles apply including balanced transfusion strategies and a restrictive use of crystalloids. That stated there are only two small prospective trials on the use of MTP in pediatrics. Hendrickson *et al*[54] described the initiation of protocol involving a fixed ratio of products based on body weight. They included 102 patients, and succeeded in transfusing at nearly a 1:1 FFP to RBC ratio, although no statistic improvement was seen in mortality (38% pre *vs* 23% post $P = 0.035$) after taking into account severity of injury. In this study only 50% of patients required a massive volume of blood (> 70 mL/kg) to be transfused this may reflect our inability to identify pediatric patient in need and not the benefit of MTP. Chidester *et al*[55] also applied the MTP principles to the pediatric population; they included 55 patients with transfusion ratios at 1:3 and similarly didn't see an improvement in mortality. They did note fewer thromboembolic complications with the MTP group (4 events *vs* 0 events).

Obstetric patients

Post-partum hemorrhage (PPH) is a major cause of up to 25% of pregnancy related deaths[56]. Physiologic changes in pregnancy including an increase in red blood cell mass (25%) and a greater increase in plasma volume (50%) allow of hemodynamic stability during the birthing process. Although changes in coagulation factors are not balanced and the relative increase in fibrinogen and factors Ⅶ, Ⅷ and Ⅸ lead to a relative hypercoagulable state[57]. These physiologic changes make the resuscitation of such patients uniquely challenging. Primary treatment of postpartum hemorrhage includes surgery and uterotonic agents. Some investigators are starting to apply balanced and goal directed resuscitation to PPH[58]. Adjuncts such as thromboelastography allow for a real-time assessment of coagulation and fibrinolysis and have allowed for targeted treatment[59,60]. Although familiarity with the normal baseline changes in the tests are key for interpretation[59]. Despite these initial advancements in PPH care, the lack of prospective data has led to limited improvement in the national management guidelines. Dahlke *et al*[61] compared management guidelines from

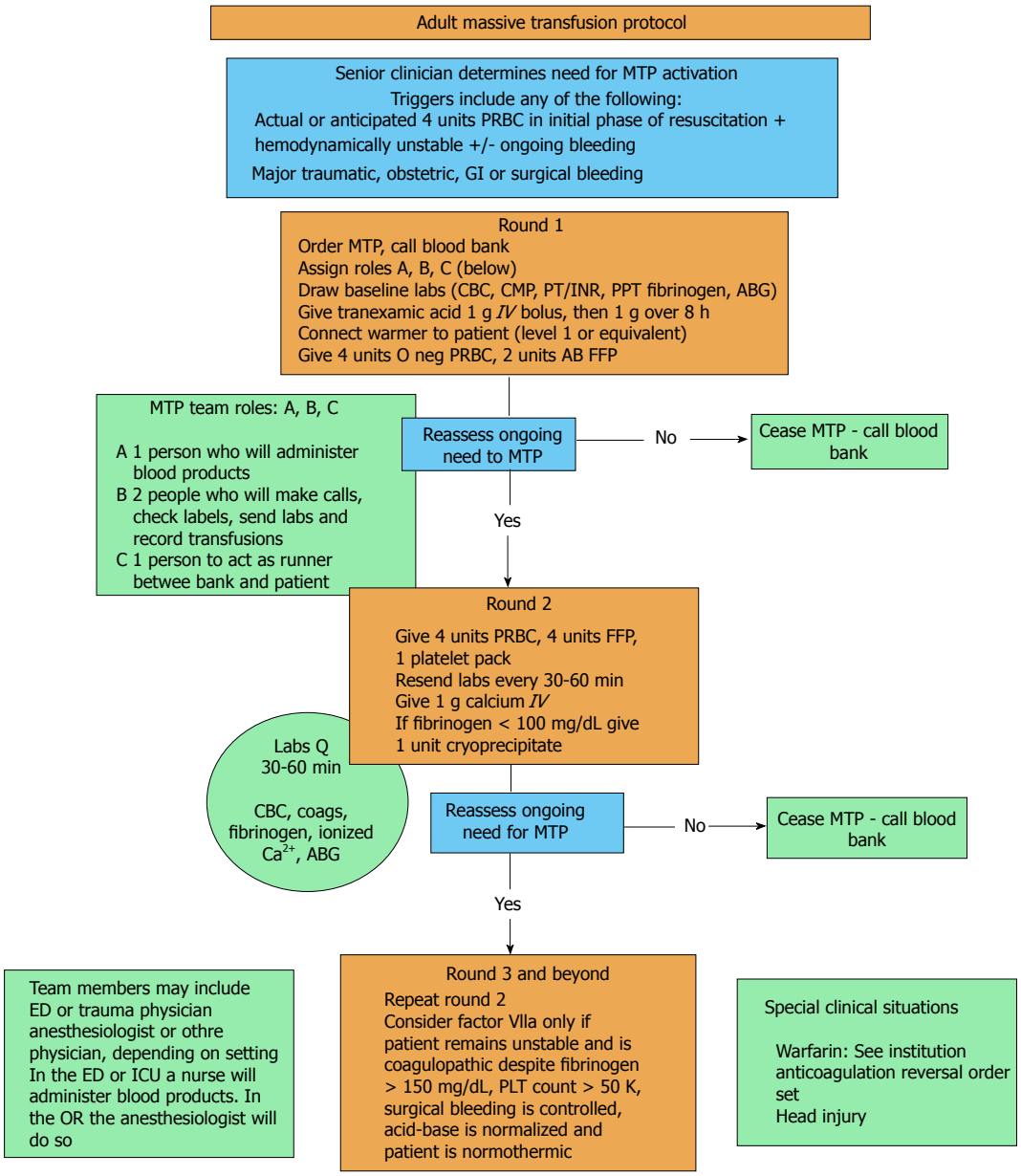

Figure 1 Our hospital-specific protocol for massive transfusion. MTP: Massive transfusion protocols; GI: Gastrointestinal; PLT: Platelet; FFP: Fresh frozen plasma; ICU: Intensive care units; PT/INR: Prothrombin time/international normalized ratio; PPTs: Pro/preplatelets; ABG: Arterial blood gas; CBC: Complete blood count; CMP: Complete metabolic panel; PRBC: Packed red blood cells; ED: Emergency department.

the 4 large nations obstetrics committees and only one guideline includes mention of blood bank notification and none describe a balanced or targeted transfusion practice. Further prospective analysis is required for the use of massive transfusion in the obstetric patient.

COMPLICATIONS OF MASSIVE TRANSFUSION

Administration of liters of inflammatory, immunomodulatory, and potentially infectious fluids into a patient already in hemorrhagic shock can assist in explanation of the common morbidities of MTP. They include: Acute respiratory distress syndrome (ARDS), transmission of viral and bacterial infection, abdominal compartment syndrome (ACS) and electrolyte abnormalities.

Lung injury

Massive resuscitation makes the lungs susceptible to the spectrum of lung injury *via* volume or immune-mediated mechanisms. For those undergoing MTP, Moss *et al*[62] found that 21% of patients will develop ARDS. The risks appear to increase with the amount of blood transfused and the mechanism of injury. Silverboard *et al*[63] demonstrated in a prospective cohort of 102 patients, development of ARDS was found at 5 or 10 units of PRBCs transfused for blunt or penetrating trauma respectively.

Infectious risk

MTP places patients at risk for both viral and bacterial

infections. In the United States, the estimated risk for HIV is 1 in 2135000. The greatest risk is for hepatitis B at 1 in 277000[64]. Patients are more susceptible to bacterial infections from platelets because of their relatively warm storage requirements (20 ℃), with an estimated risk of 1 in 5000 compared to 1 in 38500 in RBC[64]. The most common bacteria transmitted are gram-positive aerobic organisms[65].

Compartment syndrome

The incidence of intraabdominal hypertension or abdominal compartment syndrome appears to be declining with limitation and replacement of crystalloid with balanced blood products strategies. Joseph *et al*[57] showed a decrease in ACS from 7.4% to 0% with corresponding reduction in crystalloid from 12.8 to 6.6 L.

Electrolytes

Two common electrolyte abnormalities that occur in MTP are hypocalcemia, caused by the preservative citrate and hyperkalemia. Aboudara *et al*[66] show that after transfusion of 7 units of PRBCs, the patient is at risk for hyperkalemia. Furthermore, in the pediatric population, there is an association between hyperkalemia during rapid blood transfusion and cardiac arrest.

CONCLUSION

The finer points of massive transfusion, such as ratios of blood products, adjuncts, and transfusion triggers and endpoints will continue to be studied and debated in the literature for years to come. However, it cannot be argued that a massive transfusion protocol saves lives. A defined, hospital-specific MTP allows trained providers to recognize patients at risk of high-volume blood loss early, initiation of massive transfusion quickly, and has specific stop points to limit over transfusion[67]. We recommend that all centers that take care of critically ill patients of all varieties should evaluate the literature and develop their own protocol. We have included our protocol for guidance (Figure 1).

REFERENCES

1 **Callcut RA**, Cotton BA, Muskat P, Fox EE, Wade CE, Holcomb JB, Schreiber MA, Rahbar MH, Cohen MJ, Knudson MM, Brasel KJ, Bulger EM, Del Junco DJ, Myers JG, Alarcon LH, Robinson BR. Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. *J Trauma Acute Care Surg* 2013; **74**: 59-65, 67-68; discussion 66-67 [PMID: 23271078 DOI: 10.1097/TA.0b013e3182788b34]

2 **Barbosa RR**, Rowell SE, Sambasivan CN, Diggs BS, Spinella PC, Schreiber MA, Holcomb JB, Wade CE, Brasel KJ, Vercruysse G, MacLeod J, Dutton RP, Hess JR, Duchesne JC, McSwain NE, Muskat P, Johannigamn J, Cryer HM, Tillou A, Cohen MJ, Pittet JF, Knudson P, De Moya MA, Schreiber MA, Tieu B, Brundage S, Napolitano LM, Brunsvold M, Sihler KC, Beilman G, Peitzman AB, Zenait MS, Sperry J, Alarcon L, Croce MA, Minei JP, Kozar R, Gonzalez EA, Stewart RM, Cohn SM, Mickalek JE, Bulger EM, Cotton BA, Nunez TC, Ivatury R, Meredith JW, Pomper GJ, Marin B. A predictive model for mortality in massively transfused trauma patients. *J Trauma* 2011; **71**: S370-S374 [PMID: 21814106 DOI: 10.1097/TA.0b013e318227f18f]

3 **Pommerening MJ**, Goodman MD, Holcomb JB, Wade CE, Fox EE, Del Junco DJ, Brasel KJ, Bulger EM, Cohen MJ, Alarcon LH, Schreiber MA, Myers JG, Phelan HA, Muskat P, Rahbar M, Cotton BA. Clinical gestalt and the prediction of massive transfusion after trauma. *Injury* 2015; **46**: 807-813 [PMID: 25682314 DOI: 10.1016/j.injury.2014.12.026]

4 **Cotton BA**, Dossett LA, Au BK, Nunez TC, Robertson AM, Young PP. Room for (performance) improvement: provider-related factors associated with poor outcomes in massive transfusion. *J Trauma* 2009; **67**: 1004-1012 [PMID: 19901661 DOI: 10.1097/TA.0b013e3181bcb2a8]

5 **Cotton BA**, Gunter OL, Isbell J, Au BK, Robertson AM, Morris JA, St Jacques P, Young PP. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma* 2008; **64**: 1177-1182; discussion 1182-1183 [PMID: 18469638 DOI: 10.1097/TA.0b013e31816c5c80]

6 **Yücel N**, Lefering R, Maegele M, Vorweg M, Tjardes T, Ruchholtz S, Neugebauer EA, Wappler F, Bouillon B, Rixen D. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma* 2006; **60**: 1228-1236; discussion 1236-1337 [PMID: 16766965 DOI: 10.1097/01.ta.0000220386.84012.bf]

7 **Nunez TC**, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *J Trauma* 2009; **66**: 346-352 [PMID: 19204506 DOI: 10.1097/TA.0b013e3181961c35]

8 **Callcut RA**, Cripps MW, Nelson MF, Conroy AS, Robinson BB, Cohen MJ. The Massive Transfusion Score as a decision aid for resuscitation: Learning when to turn the massive transfusion protocol on and off. *J Trauma Acute Care Surg* 2016; **80**: 450-456 [PMID: 26517786 DOI: 10.1097/TA.0000000000000914]

9 **Bawazeer M**, Ahmed N, Izadi H, McFarlan A, Nathens A, Pavenski K. Compliance with a massive transfusion protocol (MTP) impacts patient outcome. *Injury* 2015; **46**: 21-28 [PMID: 25452004 DOI: 10.1016/j.injury.2014.09.020]

10 **Bhangu A**, Nepogodiev D, Doughty H, Bowley DM. Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma. *Injury* 2013; **44**: 1693-1699 [PMID: 23021369 DOI: 10.1016/j.injury.2012.07.193]

11 **Godier A**, Samama CM, Susen S. Plasma/platelets/red blood cell ratio in the management of the bleeding traumatized patient: does it matter? *Curr Opin Anaesthesiol* 2012; **25**: 242-247 [PMID: 22227445 DOI: 10.1097/ACO.0b013e32834fcc3e]

12 **Hallet J**, Lauzier F, Mailloux O, Trottier V, Archambault P, Zarychanski R, Turgeon AF. The use of higher platelet: RBC transfusion ratio in the acute phase of trauma resuscitation: a systematic review. *Crit Care Med* 2013; **41**: 2800-2811 [PMID: 23982024 DOI: 10.1097/CCM.0b013e31829a6ecb]

13 **Lal DS**, Shaz BH. Massive transfusion: blood component ratios. *Curr Opin Hematol* 2013; **20**: 521-525 [PMID: 24104413 DOI: 10.1097/MOH.0b013e3283653982]

14 **Holcomb JB**, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, Cohen MJ, Cotton BA, Fabian TC, Inaba K, Kerby JD, Muskat P, O'Keeffe T, Rizoli S, Robinson BR, Scalea TM, Schreiber MA, Stein DM, Weinberg JA, Callum JL, Hess JR, Matijevic N, Miller CN, Pittet JF, Hoyt DB, Pearson GD, Leroux B, van Belle G. Transfusion of plasma, platelets, and red blood cells in a 1: 1: 1 vs a 1: 1: 2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015; **313**: 471-482 [PMID: 25647203 DOI: 10.1001/jama.2015.12]

15 **Inaba K**, Karamanos E, Lustenberger T, Schöchl H, Shulman I, Nelson J, Rhee P, Talving P, Lam L, Demetriades D. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg* 2013; **216**: 290-297 [PMID: 23211116 DOI: 10.1016/j.jamcollsurg.2012.10.017]

16 **Cap AP**, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic acid for trauma patients: a critical review of the literature. *J Trauma* 2011; **71**: S9-14 [PMID: 21795884 DOI:

10.1097/TA.0b013e31822114af]
17 **Henry DA**, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011; **(3)**: CD001886 [PMID: 21412876 DOI: 10.1002/14651858.CD001886.pub4]
18 **Wei M**, Jian K, Guo Z, Wang L, Jiang D, Zhang L, Tarkka M. Tranexamic acid reduces postoperative bleeding in off-pump coronary artery bypass grafting. *Scand Cardiovasc J* 2006; **40**: 105-109 [PMID: 16608780 DOI: 10.1080/14017430500519864]
19 **Ker K**, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344**: e3054 [PMID: 22611164 DOI: 10.1136/bmj.e3054]
20 **Bailey AM**, Baker SN, Weant KA. Tranexamic acid for trauma-related hemorrhage. *Adv Emerg Nurs J* 2014; **36**: 123-131; quiz 132-133 [PMID: 24785665 DOI: 10.1097/TME.0000000000000018]
21 **Okamoto S**, Hijikata-Okunomiya A, Wanaka K, Okada Y, Okamoto U. Enzyme-controlling medicines: introduction. *Semin Thromb Hemost* 1997; **23**: 493-501 [PMID: 9469621 DOI: 10.1055/s-2007-996127]
22 **Roberts I**, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, Cook L, Kawahara T, Perel P, Prieto-Merino D, Ramos M, Cairns J, Guerriero C. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess* 2013; **17**: 1-79 [PMID: 23477634 DOI: 10.3310/hta17100]
23 **Morrison JJ**, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg* 2012; **147**: 113-119 [PMID: 22006852 DOI: 10.1001/archsurg.2011.287]
24 **Eckert MJ**, Wertin TM, Tyner SD, Nelson DW, Izenberg S, Martin MJ. Tranexamic acid administration to pediatric trauma patients in a combat setting: the pediatric trauma and tranexamic acid study (PED-TRAX). *J Trauma Acute Care Surg* 2014; **77**: 852-858; discussion 858 [PMID: 25423534 DOI: 10.1097/TA.0000000000000443]
25 **Stephens CT**, Gumbert S, Holcomb JB. Trauma-associated bleeding: management of massive transfusion. *Curr Opin Anaesthesiol* 2016; **29**: 250-255 [PMID: 26836808 DOI: 10.1097/ACO.0000000000000306]
26 **Ker K**, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. *BMC Emerg Med* 2012; **12**: 3 [PMID: 22380715 DOI: 10.1186/1471-227X-12-3]
27 **Perel P**, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I, Sandercock P, Shakur H, Wardlaw J. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury--a nested randomised, placebo-controlled trial. *Health Technol Assess* 2012; **16**: iii-xii, 1-54 [PMID: 22417901 DOI: 10.3310/hta16130]
28 **Schöchl H**, Solomon C, Traintinger S, Nienaber U, Tacacs-Tolnai A, Windhofer C, Bahrami S, Voelckel W. Thromboelastometric (ROTEM) findings in patients suffering from isolated severe traumatic brain injury. *J Neurotrauma* 2011; **28**: 2033-2041 [PMID: 21942848 DOI: 10.1089/neu.2010.1744]
29 **Schöchl H**, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, Arndt C, Hanke A, Voelckel W, Solomon C. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care* 2011; **15**: R83 [PMID: 21375741 DOI: 10.1186/cc10078]
30 **Aubron C**, Reade MC, Fraser JF, Cooper DJ. Efficacy and safety of fibrinogen concentrate in trauma patients--a systematic review. *J Crit Care* 2014; **29**: 471.e11-471.e17 [PMID: 24508201 DOI: 10.1016/j.jcrc.2013.12.011]
31 **Spinella PC**, Perkins JG, McLaughlin DF, Niles SE, Grathwohl KW, Beekley AC, Salinas J, Mehta S, Wade CE, Holcomb JB. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. *J Trauma* 2008; **64**: 286-293; discussion 293-294 [PMID: 18301188 DOI: 10.1097/TA.0b013e318162759f]
32 **Perkins JG**, Schreiber MA, Wade CE, Holcomb JB. Early versus late recombinant factor VIIa in combat trauma patients requiring massive transfusion. *J Trauma* 2007; **62**: 1095-1099; discussion 1099-1101 [PMID: 17495707 DOI: 10.1097/TA.0b013e31804798a4]
33 **Rizoli SB**, Nascimento B, Osman F, Netto FS, Kiss A, Callum J, Brenneman FD, Tremblay L, Tien HC. Recombinant activated coagulation factor VII and bleeding trauma patients. *J Trauma* 2006; **61**: 1419-1425 [PMID: 17159685 DOI: 10.1097/01.ta.0000243045.56579.74]
34 **Morse BC**, Dente CJ, Hodgman EI, Shaz BH, Nicholas JM, Wyrzykowski AD, Salomone JP, Vercruysse GA, Rozycki GS, Feliciano DV. The effects of protocolized use of recombinant factor VIIa within a massive transfusion protocol in a civilian level I trauma center. *Am Surg* 2011; **77**: 1043-1049 [PMID: 21944521]
35 **Boffard KD**, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, Axelsen M, Kluger Y. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* 2005; **59**: 8-15; discussion 15-18 [PMID: 16096533]
36 **Hauser CJ**, Boffard K, Dutton R, Bernard GR, Croce MA, Holcomb JB, Leppaniemi A, Parr M, Vincent JL, Tortella BJ, Dimsits J, Bouillon B. Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. *J Trauma* 2010; **69**: 489-500 [PMID: 20838118 DOI: 10.1097/TA.0b013e3181edf36e]
37 **Stanworth SJ**, Birchall J, Doree CJ, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev* 2007; **(2)**: CD005011 [PMID: 17443565 DOI: 10.1002/14651858.CD005011.pub2]
38 **Ansell J**, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 160S-198S [PMID: 18574265 DOI: 10.1378/chest.08-0670]
39 **Matsushima K**, Benjamin E, Demetriades D. Prothrombin complex concentrate in trauma patients. *Am J Surg* 2015; **209**: 413-417 [PMID: 25457236 DOI: 10.1016/j.amjsurg.2014.08.019]
40 **Nienaber U**, Innerhofer P, Westermann I, Schöchl H, Attal R, Breitkopf R, Maegele M. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. *Injury* 2011; **42**: 697-701 [PMID: 21392760 DOI: 10.1016/j.injury.2010.12.015]
41 **Berndtson AE**, Huang WT, Box K, Kobayashi L, Godat LN, Smith AM, Weingarten D, Coimbra R. A new kid on the block: Outcomes with Kcentra 1 year after approval. *J Trauma Acute Care Surg* 2015; **79**: 1004-1008 [PMID: 26488322 DOI: 10.1097/TA.0000000000000868]
42 **Hannon M**, Quail J, Johnson M, Pugliese C, Chen K, Shorter H, Riffenburgh R, Jackson R. Fibrinogen and prothrombin complex concentrate in trauma coagulopathy. *J Surg Res* 2015; **196**: 368-372 [PMID: 25881790 DOI: 10.1016/j.jss.2015.03.013]
43 **Shah A**, McKechnie S, Stanworth S. Use of Plasma for Acquired Coagulation Factor Deficiencies in Critical Care. *Semin Thromb Hemost* 2016; **42**: 95-101 [PMID: 26716502 DOI: 10.1055/s-0035-1564830]
44 **Barthel ER**, Pierce JR. Steady-state and time-dependent thermodynamic modeling of the effect of intravenous infusion of warm and cold fluids. *J Trauma Acute Care Surg* 2012; **72**: 1590-1600 [PMID: 22695427 DOI: 10.1097/TA.0b013e31824a7943]
45 **Reynolds BR**, Forsythe RM, Harbrecht BG, Cuschieri J, Minei JP, Maier RV, Moore EE, Billiar EE, Peitzman AB, Sperry JL. Hypothermia in massive transfusion: have we been paying enough attention to it? *J Trauma Acute Care Surg* 2012; **73**: 486-491 [PMID: 23019675 DOI: 10.1097/TA.0b013e31825c163b]
46 **Holcomb JB**, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, Cotton BA, Matijevic N, Muskat P, Myers JG, Phelan HA, White CE, Zhang J, Rahbar MH. The prospective, observational, multicenter, major trauma transfusion

(PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013; **148**: 127-136 [PMID: 23560283 DOI: 10.1001/2013.jamasurg.387]
47 **Murry JS**, Zaw AA, Hoang DM, Mehrzadi D, Tran D, Nuno M, Bloom M, Melo N, Margulies DR, Ley EJ. Activation of Massive Transfusion for Elderly Trauma Patients. *Am Surg* 2015; **81**: 945-949 [PMID: 26463286]
48 **Mitra B**, Olaussen A, Cameron PA, O'Donohoe T, Fitzgerald M. Massive blood transfusions post trauma in the elderly compared to younger patients. *Injury* 2014; **45**: 1296-1300 [PMID: 24560872 DOI: 10.1016/j.injury.2014.01.016]
49 **Nystrup KB**, Stensballe J, Bøttger M, Johansson PI, Ostrowski SR. Transfusion therapy in paediatric trauma patients: a review of the literature. *Scand J Trauma Resusc Emerg Med* 2015; **23**: 21 [PMID: 25888054 DOI: 10.1186/s13049-015-0097-z]
50 **Barcelona SL**, Thompson AA, Coté CJ. Intraoperative pediatric blood transfusion therapy: a review of common issues. Part II: transfusion therapy, special considerations, and reduction of allogenic blood transfusions. *Paediatr Anaesth* 2005; **15**: 814-830 [PMID: 16176309 DOI: 10.1111/j.1460-9592.2004.01549.x]
51 **Patregnani JT**, Borgman MA, Maegele M, Wade CE, Blackbourne LH, Spinella PC. Coagulopathy and shock on admission is associated with mortality for children with traumatic injuries at combat support hospitals. *Pediatr Crit Care Med* 2012; **13**: 273-277 [PMID: 21926654 DOI: 10.1097/PCC.0b013e31822f1727]
52 **Neff LP**, Cannon JW, Morrison JJ, Edwards MJ, Spinella PC, Borgman MA. Clearly defining pediatric massive transfusion: cutting through the fog and friction with combat data. *J Trauma Acute Care Surg* 2015; **78**: 22-28; discussion 28-29 [PMID: 25539199 DOI: 10.1097/TA.0000000000000488]
53 **Livingston MH**, Singh S, Merritt NH. Massive transfusion in paediatric and adolescent trauma patients: incidence, patient profile, and outcomes prior to a massive transfusion protocol. *Injury* 2014; **45**: 1301-1306 [PMID: 24950797 DOI: 10.1016/j.injury.2014.05.033]
54 **Hendrickson JE**, Shaz BH, Pereira G, Parker PM, Jessup P, Atwell F, Polstra B, Atkins E, Johnson KK, Bao G, Easley KA, Josephson CD. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. *Transfusion* 2012; **52**: 1228-1236 [PMID: 22128884 DOI: 10.1111/j.1537-2995.2011.03458.x]
55 **Chidester SJ**, Williams N, Wang W, Groner JI. A pediatric massive transfusion protocol. *J Trauma Acute Care Surg* 2012; **73**: 1273-1277 [PMID: 23064608 DOI: 10.1097/TA.0b013e318265d267]
56 **Obaid TA**. No woman should die giving life. *Lancet* 2007; **370**: 1287-1288 [PMID: 17933630 DOI: 10.1016/S0140-6736(07)61550-5]
57 **Joseph B**, Zangbar B, Pandit V, Vercruysse G, Aziz H, Kulvatunyou N, Wynne J, O'Keeffe T, Tang A, Friese RS, Rhee P. The conjoint effect of reduced crystalloid administration and decreased damage-control laparotomy use in the development of abdominal compartment syndrome. *J Trauma Acute Care Surg* 2014; **76**: 457-461 [PMID: 24398772 DOI: 10.1097/TA.0b013e3182a9ea44]
58 **Jadon A**, Bagai R. Blood transfusion practices in obstetric anaesthesia. *Indian J Anaesth* 2014; **58**: 629-636 [PMID: 25535427 DOI: 10.4103/0019-5049.144674]
59 **Ekelund K**, Hanke G, Stensballe J, Wikkelsøe A, Albrechtsen CK, Afshari A. Hemostatic resuscitation in postpartum hemorrhage - a supplement to surgery. *Acta Obstet Gynecol Scand* 2015; **94**: 680-692 [PMID: 25660118 DOI: 10.1111/aogs.12607]
60 **Long N**, Ng S, Donnelly G, Owens M, McNicholas M, McCarthy K, McCaul C. Anatomical characterisation of the cricothyroid membrane in females of childbearing age using computed tomography. *Int J Obstet Anesth* 2014; **23**: 29-34 [PMID: 24291169 DOI: 10.1016/j.ijoa.2013.07.003]
61 **Dahlke JD**, Mendez-Figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, Rouse DJ. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *Am J Obstet Gynecol* 2015; **213**: 76.e1-76.10 [PMID: 25731692 DOI: 10.1016/j.ajog.2015.02.023]
62 **Moss M**, Bucher B, Moore FA, Moore EE, Parsons PE. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA* 1996; **275**: 50-54 [PMID: 8531287 DOI: 10.1001/jama.1996.03530250054027]
63 **Silverboard H**, Aisiku I, Martin GS, Adams M, Rozycki G, Moss M. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. *J Trauma* 2005; **59**: 717-723 [PMID: 16361918]
64 **Bihl F**, Castelli D, Marincola F, Dodd RY, Brander C. Transfusion-transmitted infections. *J Transl Med* 2007; **5**: 25 [PMID: 17553144 DOI: 10.1186/1479-5876-5-25]
65 **Wagner SJ**. Transfusion-transmitted bacterial infection: risks, sources and interventions. *Vox Sang* 2005; **88**: 60 [PMID: 15663724 DOI: 10.1111/j.1423-0410.2005.00587.x]
66 **Aboudara MC**, Hurst FP, Abbott KC, Perkins RM. Hyperkalemia after packed red blood cell transfusion in trauma patients. *J Trauma* 2008; **64**: S86-91; discussion S91 [PMID: 18376177]
67 **Brown KA**, Bissonnette B, McIntyre B. Hyperkalaemia during rapid blood transfusion and hypovolaemic cardiac arrest in children. *Can J Anaesth* 1990; **37**: 747-754 [PMID: 2225291 DOI: 10.1007/BF03006533]

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