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EDITORIAL

New avenues for reducing intensive care needs in patients with chronic spinal cord injury

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Abstract

Relatively soon after their accident, patients suffering a spinal cord injury (SCI) begin generally experiencing the development of significant, often life-threatening secondary complications. Many of which are associated with chronic physical inactivity-related immune function problems and increasing susceptibility to infection that repeatedly requires intensive care treatment. Therapies capable of repairing the spinal cord or restoring ambulation would normally prevent many of these problems but, as of now, there is no cure for SCI. Thus, management strategies and antibiotics remain the standard of care although antimicrobial resistance constitutes a significant challenge for patients with chronic SCI facing recurrent infections of the urinary tract and respiratory systems. Identifying alternative therapies capable of safe and potent actions upon these serious health concerns should therefore be considered a priority. This editorial presents some of the novel approaches currently in development for the prevention of specific infections after SCI. Among them, brain-permeable small molecule therapeutics acting centrally on spinal cord circuits that can augment respiratory capabilities or bladder functions. If eventually approved by regulatory authorities, some of these new avenues may potentially become clinically-relevant therapies capable of indirectly preventing the occurrence and/or severity of these life-threatening complications in people with paraplegic or tetraplegic injuries.

Key words: Prevention of intensive care problems; Quality of care; Temporary recovery of vital functions; Micturition; Spinal networks; Central pattern generators

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Core tip: This editorial is one of the first articles to describe clearly the existence of an urgent medical need for new pharmacological products aimed at providing non-invasive solutions for spinal cord injury patients suffering chronically of urinary tract infection or pneumonia. Drugs capable of activating temporarily on demand activity in specific central networks of neurons

that control respiration or micturition are of particular interest.

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INTRODUCTION

Spinal cord injury (SCI) of traumatic origin is generally considered an irreversible condition causing, immediately after trauma, both sensory loss and mobility impairment or complete paralysis[1]. Unfortunately it often leads also, within a few weeks to a few months, to serious chronic complications among which immune problems also knows as central nervous system injury-induced immunodepression (CIDS)[2]. In fact, CIDS is probably one of the main factors contributing subsequently to the development of more specific problems such as urinary tract infections (UTIs), bed sores, pneumonia, sepsis[1]. As of now, biologics (*i.e.*, antibiotics) are generally used to treat these infections[3]. However, antibiotics are associated with the increasing problem of antimicrobial resistance and progressive lack of efficacy against infections[4]. When examined closer, different additional factors may contribute to UTIs and pneumonia specifically after SCI. For instance, descending (*i.e.*, brain and brainstem) control over the sacral spinal cord micturition center is generally lost or impaired after SCI leading to urinary retention (UR) problems[5]. When chronic UR is found, the bladder remains full, although leaking may occur (associated also with bladder sphincter dyssynergia), and overgrowth of bacteria is regularly diagnosed, contributing directly to recurrent UTIs[6]. In the case of pneumonia, specifically for those with tetraplegia (but not only), breathing control problems and reduced coughing capabilities have a direct impact upon mucus accumulation and bacterial overgrowth that leads to pneumonia and, sometimes, respiratory failure[7].

INADEQUACY OF CURRENTLY USED APPROACHES

Medical devices for managing bladder problems are probably the most extensively used means to prevent UTIs. Chronic indwelling catheters or intermittent catheters are typically used for regular bladder drainage and, hence, for reducing incidence of bacterial overgrowth. However, the use of catheters also contributes to UTIs. When chronically performed, these devices are associated with multiple problems including pyuria, pericatheter sepsis, haemorrhage, or bladder and kidney damage[8]. Other alternative approaches are occasionally used such as drugs with peripheral actions on bladder contraction, electrostimulation of sacral anterior roots, diapers or condom sheaths although UR remains largely an unmet medical need that is generally life-threatening[8,9]. For respiratory problems and mucus accumulation, mainly mechanical approaches are normally used, *i.e.,* physical therapy, spontaneous or mechanically assisted coughing, suctioning, and mechanical insufflation-exsufflation[10]. These procedures are rather complex, time-consuming and expensive (*i.e.,* both labor and specialized medical devices)[11].

CENTRALLY-ACTING PHARMACOLOGICAL APPROACHES

There is compelling evidence suggesting that lower incidence of pneumonia or UTIs may be found if, respectively, cardiovascular and pulmonary function or bladder function could be stimulated and improved. To investigate that, some researchers are exploring a novel approach essentially based on central (spinal cord) small molecule therapeutics stimulation of neuronal networks known to normally (*i.e.,* in absence of spinal injuries) control either respiration or micturition.

Proof-of-concept data demonstrating the efficacy of restoring corresponding spinal neuronal activity on voiding reflex have been reported in animal models of SCI. Serotonergic drugs such as 5-HT1A and 5-HT7 agonists were shown indeed, following a single intravenous (*i.v.*) administration, to augment acutely micturition reflex and voiding despite the lack of brain control over that same spinal network in paraplegic rats[12,13]. Central actions upon sacral neuronal networks has been clearly shown by Lecci *et al*[14] following intrathecal administration of similar compounds[14]. My own research group in Canada has built upon these findings to show recently that powerful synergistic effects on reflex voiding may be found by co-administration subcutaneously of 5-HT1A and 5-HT7 receptor agonists in paraplegic mice[15]. Comparable voiding-activating has been shown using direct electrical stimulation of corresponding spinal cord areas in anesthetized chronic paraplegic cats[16].

For breathing problems, the role of another set of neurons has been explored using a comparable approach. It is the crossed phrenic pathway in the spinal cord, also known as CPP, that exhibit significant control of phrenic motoneurons and nerves for diaphragm contraction. It had been found originally by the French researchers Aubier and Pariente, that *i.v.* infusion of aminophylline, an adenosine receptor antagonist, can improve ventilation in dogs *via* stronger diaphragmatic contraction[17]. However, Nantwi *et al*[18] more recently showed that adenosine antagonists aminophylline or theophylline can augment respiration by acting centrally although some additional peripheral actions upon the diaphragm cannot be excluded. Theophylline and aminophylline have both been considered as relatively safe

since approved already by FDA as treatment against chronic obstructive pulmonary disease. Other drugs such as 5-HT1A agonist administered *i.p.* to chronic paraplegic rats have been shown also to stabilize ventilator abnormalities[19]. However, clinical efficacy against respiratory problems and related consequences on mucus accumulation and pneumonia with adenosine antagonists or 5-HT1A agonists remains to be shown.

CONCLUSION

No safe or acceptable treatments have yet been found against the occurrence or severity of significant health concerns such as UTIs and pneumonia in chronic SCI patients. Non-invasive and user-friendly pharmacological acting centrally upon specific spinal command centers involved in controlling micturition and breathing may eventually constitute safe and potent treatments against recurrent infections associated with chronic UR and breathing insufficiency after SCI.

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MINIREVIEWS

Clinical decision support for drug related events: Moving towards better prevention

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Abstract

Clinical decision support (CDS) systems with automated alerts integrated into electronic medical records demonstrate efficacy for detecting medication errors (ME) and adverse drug events (ADEs). Critically ill patients are at increased risk for ME, ADEs and serious negative outcomes related to these events. Capitalizing on CDS to detect ME and prevent adverse drug related events has the potential to improve patient outcomes. The key to an effective medication safety surveillance system incorporating CDS is advancing the signals for alerts by using trajectory analyses to predict clinical events, instead of waiting for these events to occur. Additionally, incorporating cutting-edge biomarkers into alert knowledge in an effort to identify the need to adjust medication therapy portending harm will advance the current state of CDS. CDS can be taken a step further to identify drug related physiological events, which are less commonly included in surveillance systems. Predictive models for adverse events that combine patient factors with laboratory values and biomarkers are being established and these models can be the foundation for individualized CDS alerts to prevent impending ADEs.

Key words: Drug-related side effects and adverse reactions; Decision support systems; Clinical; Medication errors; Patient safety; Clinical pharmacy information systems; Intensive care units; Critical care; Adverse drug event; Clinical decision support systems

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Core tip: Drug related events in the intensive care unit are associated with higher medical costs and dire patient outcomes. Clinical decision support (CDS) systems are the most important component to aid in adverse drug event (ADE) surveillance and improve in medication safety. Institutions are increasing the use of CDS systems for event detection and CDS systems that combine patient factors with laboratory values, drug information and biomarkers are key to effective ADE prevention.

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INTRODUCTION

Medication errors (ME) occur at median rate of 106 per 1000 patient days in adult intensive care unit (ICU) patients[1]. ME are concerning because of the prospect of impending injury, known as a preventable adverse drug event (ADE). Table 1 provides definitions of drug related events[2-6]. Approximately one-third of ME result in ADEs[7,8]. Examples of ME resulting in ADEs include missed doses, wrong administration technique, duplicate therapies, drug interactions, equipment failure, inadequate monitoring and preparation errors[9].

Critically ill patients are at greater risk for MEs and ADEs compared to non-ICU patients because of the complexity of their drug regimens, sheer volume of medications that they receive, in particular, the volume of intravenous drugs received and acute changes in organ function that can alter the pharmacokinetics[8,10,11]. Prevention of ME and ADEs is important and the significance can resonate to a greater degree in critically ill patients because the severity of ADEs and related outcomes are worse compared to patients in other settings[8,12-14].

Institutions need to commit to an active medication safety surveillance system to detect and prevent drug related events and ensure the safest care possible[15]. Active medication safety surveillance systems use methods that can be categorized as: (1) retrospective approaches that are conducted after drug related events occur and often after the patient is discharged from the hospital; or (2) prospective approaches that capture events in real-time or as close to real-time as possible allowing for interventions to prevent the event from progressing to harm[16]. Voluntary reporting or incident reporting is the most commonly used retrospective surveillance method[17]. Retrospective methods also include non-targeted and targeted medical record reviews. While non-targeted medical record reviews encompass a detailed look at all patient data, a targeted medical record review such as one using a trigger tool focuses on a review of a particular set of patients[18]. Alternatively a targeted medical record review can focus on a particular section of the chart such as the discharge summary[19]. Prospective methods frequently rely on automated systems using clinical decision support (CDS).

CDS systems improve treatment outcomes and patient care by providing clinicians with patient-specific information that is intelligently filtered and presented at relevant times[20]. CDS is defined as "computer software employing a knowledgebase designed for use by a clinician involved in patient care, as a direct aid to clinical decision-making"[21,22]. CDS is typically incorporated as part of a computerized prescriber order entry (CPOE) system and is used to facilitate prevention of ME and ADEs. This system is used to provide feedback to clinicians through alerts and reminders when triggered by certain information available in electronic format[23]. CDS is more effective than voluntary reporting at identifying ADEs with only 1% of those events identified with CDS provided as incident reports[24]. Although overlap between voluntary reporting and automated CDS for ADE detection is reported as high as 13%[25]. Jha *et al*[24] demonstrated that CDS is more efficient than non-targeted medical record review requiring one-fifth less time to complete ADE surveillance: 11 h/wk *vs* 55 h/wk, respectively. It was also noted that while CDS identified slightly fewer events, the ADEs identified were different between methods, asserting that CDS is a necessary adjunct to medical record review. Overall, CDS is faster, less expensive and can identify ADEs not typically detected by clinicians when compared with voluntary reporting[26-31].

Many hospital systems are moving towards adopting electronic health records with meaningful use guidelines and incentives provided by the Center for Medicare and Medicaid Services, and this is enhancing the incorporation of CDS in patient care[32]. A 2015 survey[33] indicated 94.1% of hospitals adopted an electronic health record. This is important because collecting patient data electronically and applying systems to screen these data for ADEs are the initial steps to develop effective safety surveillance[29]. The same survey reports 80.9% of hospitals employ an inpatient CPOE system with CDS, a remarkable 78.2% increase since 2003[33]. In this article, we discuss the effective use of CDS for detecting ME and ADEs, then we will propose ways to use CDS for the prevention of ADEs to further enhance the safety of patients.

Table 1 Definitions of drug related events

Term	Definition
Medication error[2]	"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. This may include errors in prescribing, distribution, administration and monitoring"
Adverse drug reaction[3]	"Any undesired, unexpected, or unintended outcome associated with drug use"
Drug-related hazardous condition[3,4]	"Is the antecedent to injury or the temporal gap between the identification of an adverse drug reaction and the drug induced injury". It occurs in the presence or absence of a medication error
ADE[5]	"Injury associated with the use of a drug"
Preventable ADEs[6]	"Injury associated with a medication error"
Potential ADEs[5]	"Medication errors with the potential to cause harm, but harm does not actually occur. Potential ADEs can be further described as intercepted and non-intercepted"
Trigger[6]	"Signals or clues used to identify adverse events"

ADE: Adverse drug event.

DETECTION OF ME AND ADES USING CDS

CDS systems are effective at detecting potential ME and alerting prescribers so that appropriate evaluation and action can be taken. Healthcare providers are inconsistent in the identification of ME because of personal knowledge, previous experience and timing of the medication order review; therefore, it is essential to have a reliable surveillance system to aid in identification[34]. Raschke *et al*[35] reported that 44% of ME would have been missed without the use of CDS. Further, a systematic review of studies evaluating CDS alerts generated in response to drug dose selection for patients with acute kidney injury (AKI) demonstrated that 17 out of 19 studies effectively detected ME allowing for intervention with the implementation of CDS[36]. The thought is that detection of ME with CDS due to scenarios such as inappropriate dosing based on age, weight, underlying condition and renal function will allow for intervention and prevention of potential ADEs.

An effective tool to assist with adverse event identification is the Institute for Healthcare Improvement Trigger Tool that contains a specific module focused on ADEs[6]. The trigger tool demonstrates utility as it was used to detect 230 ADEs in 1009 ICU patient days in 79 patients[14]. Interestingly in this study, only the three triggers were responsible for detecting 78% of ADEs. While the trigger tool was evaluated manually, the triggers can be used as the knowledge or signals for the development of automated alerts using CDS.

Classen *et al*[25] developed a clinical event monitor allowing for detection of ADEs using automated trigger or alert. An alert was sent to the physician when there was a potential for an ADE, upon confirmation of the ADE, the medication(s) were stopped, substituted or an antidote was given if needed. In this 18-mo study, 631 of 731 ADEs identified were detected using automated CDS with the majority of ADEs described as moderate or severe.

While research shows that automated CDS alerts are useful in the clinical setting, alerts for ADE detection can be ineffective at preventing harm because alerts are generated with minimal time for intervention or more often alerts are generated after the patient is already experiencing an ADE. This is apparent in the use of the alerts targeted at antidote administration designed for detection and not prevention since the event is already in the midst of treatment. Table 2[17,37-39] provides examples of alerts designed for event detection. Another type of alert geared to detection are abnormal laboratory value alerts with thresholds that exceed the recommended laboratory limit or higher. Alert thresholds with abnormal values higher than acceptable are often targeted at high specificity and low sensitivity, thus possibly reducing alert fatigue but limiting the value in ADE prevention[40]. Still antidote alerts and alerts set with a high abnormal laboratory value thresholds can be useful in understanding the environment, providing an opportunity to assess for causal factors and preventing future events through systematic changes[37]. It can even be beneficial to identify non-preventable ADEs using CDS systems to mitigate the intensity of the injury[9].

ADE PREVENTION CONSIDERATIONS FOR ALERT DEVELOPMENT

The next step in CDS advancement is predicting impending injury/end-organ damage and identifying events using pre-emptive triggers with ample time to intervene. This is the ideal application of a drug related hazardous condition (DRHC), which is the early identification of a drug-related event before the ADE occurs[3,4]. Ten drugs are responsible for over sixty percent of preventable ADEs, including anticoagulants, opiate agonists, and insulin[41]. This suggests that ADEs are not as random as one thinks and it is practical to use this information to build effective CDS. Also, these preventable events are triggered by the progressive decline in laboratory and physiologic markers allowing time for intervention and prevention of harm.

CDS that generates alerts to prevent ADEs utilizing patient laboratory values and drug information has great potential to improve patient outcomes. For example, Moore *et al*[42] suggests to create an alert to prevent a

Table 2 Examples of alerts designed to detect drug-related events

Ref.	Alert designed for detection
Stockwell *et al*[37]	Abnormal laboratory value exceeding recommended upper limit
	Examples
Harinstein *et al*[38]	ACE inhibitor/ARB and patient's serum potassium is > 6 mmol/L
	INR > 4 and on warfarin
	Blood glucose < 40 mg/dL and on antidiabetic agent
	Platelet count < 50000/mm^3 and on a drug that causes thrombocytopenia
Kane-Gill *et al*[39]	Unexpected discontinuation of drug
Kane-Gill *et al*[17,39]	Antidote evaluations such as flumazenil, naloxone, sodium polystyrene, protamine, dextrose 50%; lepirudin use; argatroban use

ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; INR: International normalized ratio.

severe hypoglycemic state by warning when the occurrence of three consecutive low glucose occurs in the presence of a new anti-diabetic medication. The alert should be generated as the glucose levels deteriorate, even before the patient reaches an unacceptable glucose level and experiences mental status changes. Another example of a prevention alert is a patient that does not have a bowel movement in 24 h following initiation of an opioid. In this scenario, there is no need to wait until the patient becomes impacted if a bowel stimulant is begun. Using CDS to generate alerts for ADE prevention have been tested with success[9,35,42-48]. More examples of preventative alerts are provided in Table 3.

MOVING TOWARDS BETTER ADE PREVENTION

Percent change in laboratory values instead of absolute cut points and trajectory analysis

Movement in the area of ADE prevention requires clinicians to change the mindset of specific cut points in the laboratory values and consider percent change and percent change over time when appropriate. An example of this is identifying drug induced AKI. Previous CDS alerts were built on an absolute serum creatinine value of $\geqslant$ 1.5 mg/dL or an absolute increase in serum creatinine of 0.5 mg/dL[49,50]. This approach does not account for the patient's baseline serum creatinine and is likely to miss important events in patients with low baselines (*e.g.*, young women, vegetarians) or result in false positives in patients with underlying chronic kidney disease. Others have applied knowledge to signal an alert at a 50% increase in serum creatinine from baseline; however, that may miss small changes in serum creatinine and miss opportunities for early intervention[51]. Recent alerts are designed on the Kidney Disease Improving Global Outcomes (KDIGO) criteria or the serum creatinine component of the KDIGO criteria when urine output is unavailable[52,53]. According to the KDIGO guidelines, a patient is classified as AKI stage 1 if there is a 0.3 mg/dL increase in serum creatinine in 48 h or an increase in serum increase of 1.5-1.9 times baseline in 7 d. This abrupt change considers time and baseline values providing a more detailed assessment of kidney function and opportunities for early alert and interventions. If a baseline serum creatinine is unavailable, then there are methods of estimation to consider[54]. Stage 2 and Stage 3 AKI alerts per KDIGO may not provide opportunity for prevention but appropriate management at this point may mitigate severity and prevent permanent injury.

The concept of trajectory analysis applied to alerts would allow for a pre-emptive alert to be generated when there is a percent change in the laboratory value over a specified period. This would predict that the laboratory value would eventually be out of an acceptable range before it actually reaches the unacceptable range. Signals for alerts are set to a triglyceride of > 400 mg/dL (unacceptable range) when receiving propofol. There would be an advantage to scanning for a percent increase over a couple of days instead of waiting for the absolute number to be achieved. Importantly, this could be applied to abnormal international normalized ratio (INR) values for patient receiving warfarin. Waiting until an INR of 4 or 5 occurs before being alerted could waste valuable time in preventing an ADE, instead a 20% rise daily over 3 d could be a preventative trigger. This concept could also be applied to drug concentrations. The key to the successful use a trajectory analysis will be supporting the percent change as clinically meaningful by selecting percent changes relative to the occurrence of an ADE. Table 4 provides an example of using percent change for drug-induced thrombocytopenia instead of applying an absolute cut point[38].

Biomarkers

The use of DRHCs or biochemical, physiologic, or clinical status change caused by medications, portending further injury is sometimes difficult when our biomarkers lag behind the actual injury[3,4]. This is true in the case of AKI. Generating an alert after identifying a spike in serum creatinine may be too late as there is already significant damage and loss of kidney function[55].

Cystatin C, is a better detector of kidney injury when compared with serum creatinine and some research suggests that serum cystatin C can discriminate between patients that develop AKI and patients whose serum creatinine will return to baseline in 48 h[55]. This biomarker shows promise for early detection and earlier intervention. Additionally, a study by Frazee *et al*[56] shows that biomarkers can also improve drug dosing. This study showed that vancomycin dosing in the ICU can be improved 2.5 fold when using cystatin C and serum creatinine to estimate GFR as opposed to just serum creatinine alone[56]. Interestingly, some biomarkers can also identify the type of kidney injury and the location of damage. If these are included in the signals for alert generations, clinicians will be able to

Table 3 Examples of preventative alerts

Ref.	Drug related hazardous condition for alert detection	Adverse drug event prevention	Criteria for prevention alert
Rommers *et al*[43]	Before a DRHC occurs-eventually hemoglobin drop	Bleed	Elderly patient who is not taking a PPI and is started on an NSAID
Moore *et al*[42]	Hypoglycemia	Mental status changes	Receiving a new antidiabetic agent and 3 consecutive low glucose results that are steadily declining over a period of time
Moore *et al*[42]	Hypokalemia	Dysrhythmia	Drug started causing hypokalemia + potassium level under 3.8 mEq/L
Moore *et al*[42]	Thrombocytopenia	Bleed	Drug started causing thrombocytopenia and platelets slowly decrease over 50000/mm^3 within 4 d
Moore *et al*[42]	Hyperkalemia	Dysrhythmia	Drug started causing hyperkalemia + potassium level over 5.5 mEq/L and increasing slowly over 72 h
Raschke *et al*[35]	C. difficile	Permanent gastrointestinal disorders (*i.e.*, irritable bowel syndrome, colectomy)	Antidiarrheal and recent aggressive antibiotic therapy OR history of Clostiridum difficile
Rommers *et al*[43] and Silverman *et al*[44]	Before DRHC occurs-eventually digoxin level elevated	Dysrhythmia, confusion	Patient with 3 consecutive increasing serum creatinine levels and also on digoxin therapy (or other renally cleared drugs would apply such as metformin, enoxaparin, vancomycin)
Rommers *et al*[43]	Constipation	Bowel obstruction	Narcotic started recently and patient has a history of constipation or narcotic started recently and patient has not had a bowel movement in over 24 h
Van Doormaal *et al*[45]	Constipation	Bowel obstruction	Opioid prescribed without a co-prescription of a stimulant laxative
Van Doormaal *et al*[45]	KDIGO stage 1 AKI-in the future biomarkers may be the early sign of AKI before SCr rise	KDIGO stage 3 AKI	Sulfonamide urea derivate is prescribed and the patient has a creatinine clearance of less than 10 mL/min
DiPoto *et al*[46]	Before a DRHC occurs-eventually hemoglobin drop	Bleed	Patient has epidural and started on an anticoagulant or antiplatelet
DiPoto *et al*[46]	Sedation	Mental status changes	Fentanyl patch and no documented history of long-acting opioid use
Silverman *et al*[44] and Jha *et al*[47]	ALT rising	Hepatic failure	Hepatotoxic drug and ALT increase by 20%
Silverman *et al*[44] and Jha *et al*[47]	Osmolarity increasing	Mental status changes, risk of death	Lorazepam use and osmolarity increasing

DRHC: Drug related hazardous condition; KDIGO: Kidney Disease Improving Global Outcomes; AKI: Acute kidney injury; ALT: Alanine aminotransferase.

make a quicker treatment decisions.

Another biomarker panel that is currently available in clinical practice is urinary tissue inhibitor of metalloproteinase (TIMP-2) and insulin-like growth factor-binding protein (IGFBP7). This combination of biomarkers available in Nephrocheck™ predict patients at risk for developing AKI within 12 to 24 h following sample collection[57]. This makes TIMP-2/IGFBP7 a valuable marker to consider when designing preventative alerts in the future as we learn about the impact of using these biomarkers on patient care.

Drug induced liver injury also continues to be problematic, and clinicians can benefit from early identification of this injury. Research continues to find biomarkers to indicate drug injury such as microRNAs and serum metabolites presenting as better indicators than ALT[58]. Biomarkers, such as the ones discussed above, can be employed in the future to guide clinicians in making early interventions with CDS alerts.

Drug combinations

The risk of an ADE may change when drugs are combined. Non-critically ill children receiving aminoglycosides or other nephrotoxins for more than 3 d in the hospital are at risk for drug induced AKI[59]. AKI can be prevented by using CDS to alert clinicians when patients receive 3 or more nephrotoxins followed by close monitoring of serum creatinine[59]. This CDS application resulted in improved patient outcomes including a 42% decrease in the observance of AKI intensity[60]. Future studies need to test this CDS in critically ill and non-critically ill adults. Constructing alerts based on thoughtful consideration of high-risk drug combinations has the potential to prevent ADEs.

Drug induced physiologic events

As noted, the majority of CDS for ADE prevention includes abnormal laboratory concentrations as the trigger for an alert. Less frequently, hospitals report surveillance of drug-induced physiologic events[17]. In general, we have created better CDS to identify patients undergoing clinical deterioration or at the first signs of sepsis by incorporating blood pressure, heart rate and respiratory rate into alerts[61,62]. Physiologic parameters such as blood pressure are drug induced and can be the next set of preventative ADE alerts we develop to improve patient care[3].

Predictive analytics and forecasting models

Using a holistic approach to predict the risk of disease

Table 4 Alerts to predict an impeding adverse drug event using percent changed in the laboratory value

Ref.	Drug related hazardous condition for alert detection	Adverse drug event preventing	Criteria for prevention alert
Harinstein *et al*[38]	Platelet drop	Bleed	⩾ 50% decrease in platelets between most recent and second most recent platelet count
Harinstein *et al*[38]	Platelet drop	Bleed	2 consecutive decreases in platelets with ⩾ 25% difference between the third most recent and the most recent platelet count

Table 5 Summary of proposed approaches to developing clinical decision support to prevent adverse drug events

Proposed approach	Description
Trajectory analysis	Identify laboratory values as they are on the incline or decline before they reach a critical value
Biomarkers	Use biomarkers that identify patients at risk for organ damage
Drug combinations	Generate alerts for drug combinations that place the patient at risk for drug-induced injury
Drug induced physiologic events	Add alerts for possible drug induced alterations in physiologic parameters to clinical decision support
Predictive analytics and forecasting models	Develop models that predict possible drug induced injury based on risk factors and use this information for advanced alerts using machine learning for adaptive response

may be the best way to prevent unfavorable health outcomes, such as ADEs. In the case of AKI, many predictive models have been developed, though not necessarily in the critical care setting where there is a need[63,64]. Variables included in predictive models are age, gender, race, co-morbidities and acute conditions. Combining known patient risk factors with laboratory data and biomarkers would make an ideal predictive model and aid in preventative ADE alert development. This model also could employ machine learning techniques and incorporate population/region specific data to better predict patient risk and outcomes to accommodate adaptive changes (Table 5).

CONCLUSION

The concern for harmful outcomes associated ADEs, especially preventable ADEs makes reliable and effective CDS systems a necessary addition for surveillance, especially for critically ill patients. CDS systems can be used to further improve patient outcomes when directed at preventing ADEs and moving beyond detection. CDS designed to generate alerts portending injury allows providers time for intervention. Studies designed to maximize the benefit of preventative alerts and determine the impact on patient outcomes are needed.

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ORIGINAL ARTICLE

Case Control Study

Interprofessional, multiple step simulation course improves pediatric resident and nursing staff management of pediatric patients with diabetic ketoacidosis

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Abstract

AIM

To investigate the use of a multidisciplinary, longitudinal simulation to educate pediatric residents and nurses on management of pediatric diabetic ketoacidosis.

METHODS

A multidisciplinary, multiple step simulation course was developed by faculty and staff using a modified Delphi method from the Pediatric Simulation Center and pediatric endocrinology department. Effectiveness of the simulation for the residents was measured with a pre- and post-test and a reference group not exposed to simulation. A follow up post-test was completed 3-6 mo after the simulation. Nurses completed a survey regarding the education activity.

RESULTS

Pediatric and medicine-pediatric residents (n = 20) and pediatric nurses (n = 25) completed the simulation course. Graduating residents (n = 16) were used as reference group. Pretest results were similar in the control and intervention group (74% ± 10% *vs* 76% ± 15%, P = 0.658). After completing the intervention, participants improved in the immediate post-test in comparison to themselves and the control group (84% ± 12% post study; P < 0.05). The 3-6 mo follow up post-test results demonstrated knowledge decay when compared to their immediate post-test results (78% ± 14%, P = 0.761). Residents and nurses felt the inter-disciplinary and longitudinal nature of the simulation helped with learning.

CONCLUSION

Results suggest a multidisciplinary, longitudinal simulation improves immediate post-intervention knowledge but important knowledge decay occurs, future studies are needed to determine ways to decrease this decay.

Key words: Interdisciplinary; Education; Simulation; Diabetic ketoacidosis; Pediatrics

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Core tip: Our paper describes how an interprofessional simulation improved the understanding of the medically complex disorder of pediatric diabetic ketoacidosis (DKA). This was shown in our data collection both by improvements in test scores from pre-simulation to post-simulation, as well as when compared to the control group. Few studies have looked at simulation as an educational tool for DKA. Our simulation course identified gaps in knowledge, communication, and patient care. Therefore, demonstrating that interprofessional simulation is a useful tool to teach a team based approach and focus on communication between nursing staff and physicians when taking care of critically ill children.

Larson-Williams LM, Youngblood AQ, Peterson DT, Zinkan JL, White ML, Abdul-Latif H, Matalka L, Epps SN, Tofil NM. Interprofessional, multiple step simulation course improves pediatric resident and nursing staff management of pediatric patients with diabetic ketoacidosis. *World J Crit Care Med* 2016; 5(4): 212-218 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/212.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.212

INTRODUCTION

Diabetic ketoacidosis (DKA) is a life threatening condition that results from a lack of insulin and one of the more common causes of pediatric intensive care unit (ICU) admissions[1-4]. Without insulin, counter-regulatory hormones increase leading to an accelerated, potentially fatal, catabolic state[5-7]. If treatment including insulin, electrolyte replacement, and fluids are administered appropriately, the catabolic process can be reversed[6-8]. DKA occurs in approximately 29% of patients with new onset type 1 diabetes mellitus and in 10% of patients with new onset type 2 diabetes mellitus[4,6]. Mortality related to DKA is less than 5% with 90% due to cerebral edema[1,3,4,6,7]. Other complications that increase risk for morbidity and mortality include electrolyte abnormalities, acute renal failure and acute pancreatitis[1,5,7]. In order to decrease these, early recognition and appropriate ICU management is required[4,6-9].

Resident education of DKA largely consists of lectures, reading articles, and informal instruction from pediatric faculty and senior residents. Nursing education is less formal, often through self-directed learning, computer-based training and informal bedside teaching. Simulation based learning is an effective tool to supplement traditional teaching methods due to it providing a safe learning environment learners, incorporating aspects of adult learning theory and promoting multidisciplinary learning[10-15].

In an effort to standardize DKA education and focus on interprofessional teaching, we created a multistep, longitudinal simulation course. The scenario begins at diagnosis of DKA, proceeds through a standardized treatment course including management of fluids, insulin, electrolyte replacement, monitoring for complications, and finishes when the patient transitions to subcutaneous insulin. Our primary hypothesis is that pediatric residents exposed to this multidisciplinary, longitudinal simulation improve their DKA knowledge compared to our reference group, graduating senior

residents not exposed to the intervention. Our secondary hypothesis is that by conducting the intervention in an inter-disciplinary fashion, both nurses and physicians will better understand each other's roles in the care of patients with DKA.

MATERIALS AND METHODS

Subjects

Pediatric and combined medicine/pediatric residents participated in the simulation course as part of their scheduled endocrinology rotation and were invited during their elective rotations if they were not already scheduled for endocrinology. Graduating third year pediatric residents and fourth year medicine/pediatric residents prior to initiation of this course were the reference group. Pediatric nurses from the intensive care unit and step down unit participated with the residents. Sessions were conducted approximately once a month from September 2013 through March 2015.

Description of protocol/scenario development

The research was approved by Institutional Review Board at the University of Alabama in Birmingham. A scripted scenario was developed by simulation and endocrinology experts by a modified Delphi process to provide a uniform educational experience for our participants. An accelerated time sequence was used. The scenario was a patient with new onset diabetes in DKA. Once the diagnosis was confirmed, a plan of care was constructed with the nurses to include patient monitoring, administration of medications, correction of electrolyte imbalances, and schedule for lab draws. Participants were required to manage electrolyte abnormalities, administer appropriate fluid management, and monitor glycemic control while on an insulin drip. All participants were confronted with development of cerebral edema during the care of their patient. The simulated patient's response was based on the provider's reactions to changes in labs and clinical course. Actions performed were documented using a structured checklist created by endocrinologists. Once the patient met appropriate criteria, the resident provided instruction to the nurses regarding transition to subcutaneous insulin. Following the case, there was a participant-centered debriefing led by a content expert in pediatric endocrinology and a simulation nurse educator. Key points in the diagnosis and management of DKA were covered.

Outcome measures

The effectiveness of the simulation for the residents was measured based on a pre- and post-test created by endocrinology and educational experts. Participants completed a pre-test prior to the simulation (Table 1). The same post-test was given immediately after completion of the simulation and a second retention post-test was administered three to six months after the course. The reference group completed the same test in their last month of residency. The nursing staff completed a survey following the conclusion of the scenario and debriefing session.

Statistical analysis

Statistical analysis was performed using SPSS software (Chicago, IL). A χ^2 test evaluated for categorical differences between the intervention and reference groups of residents. Paired and unpaired *t* tests compared test scores both within the intervention group and reference group respectively. A *P* value of < 0.05 was considered statistically significant. Feedback comments were evaluated for common themes.

RESULTS

Forty-five subjects participated including twenty residents and twenty-five nurses. Seventeen monthly sessions were conducted. The reference group was 72% (16/22) of senior residents in their last month of training (June 2013). No personal history of diabetes mellitus type 1 was reported. Only one participant cared for a family member with diabetes. Exposure to these patients prior to the simulation was not significantly different amongst the two populations. Table 2 shows the demographics.

There was no statistical difference between the reference group's knowledge assessment test and the intervention group's pre-test, 75% ± 10% *vs* 77% ± 15%, $P = 0.66$. Figure 1 shows the assessment scores of the intervention group at the three time periods tests; pre-test, initial post-test and 4-6 mo follow-up test. There was a significant improvement after the intervention but knowledge decay at the follow-up assessment. In addition, the intervention group had significant improvement in their test scores when compared to the reference group after the intervention (75% ± 10% *vs* 84% ± 12%, $P = 0.02$). While overall score did not improve between the pre-test and the second post-test in the simulation group, specific questions involving fluid management and cerebral edema noted sustained improvement. This improvement is also noted when compared to the reference group.

No insulin or bicarbonate boluses were administered during any of the simulation activities. Only four participants administered more than one fluid bolus. All participants recognized the possibility of cerebral edema and 80% (16/20) of residents communicated this to the parent. Only half completed a neurological exam despite the concern for cerebral edema.

Ninety-two percent (23/25) of nurses were from the step down ICU and 8% (2/25) were from the pediatric ICU. The majority were new critical care nurses with 80% (20/25) having < 5 years of experience. Sixty-four percent of (16/25) cared for < 5 patients per month with DKA. All nursing participants found the experience positive and provided a better understanding of the diagnosis and management of DKA. Ninety-six percent (24/25) of believed the simulation to be more beneficial

Table 1 Demographic and test questions

Demographic information

1 What year in residency are you?
PGY1 PGY2 PGY3 PGY4
2 Circle the residency program you are currently enrolled in.
Pediatrics Med-Peds Emergency medicine
3 Have you done an endocrine rotation during your residency?
Yes No
(1) If yes, what year in your training did you do this rotation?
PGY1 PGY2 PGY3 PGY4
4 Do you personally have type 1 diabetes?
Yes No
(1) If yes, have you ever been treated for DKA?
Yes No
5 Have you ever actively cared for a family member or close friend with diabetes?
Yes No
6 Have you ever cared for a patient with DKA during your training?
Yes No
(1) If yes, what rotations did you take care of these patients? Please list the rotations
(2) Approximately how many patients have you cared with DKA
0-5 patients 5-10 patients 10-20 patients > 20 patients

Test questions ([1]correct answers, some questions have more than one answer)

1 Match the best words that define diabetic ketoacidosis (DKA) with the appropriate lab value

A Dehydration	(1) BS > 200 mg/dL[1]
B Ketosis[1]	(2) Bicarb < 19, Ph < 7.35
C Acidosis[1]	(3) Urine or serum ketones[1]
D Polydipsia	(4) Bicarb < 15, pH < 7.3[1]
E Vomiting	(5) Spec grav > 1.030
F Hyperglycemia[1]	(6) Glycosuria

2 Which of the following signs/symptoms best describes a patient with DKA?
A Vomiting/diarrhea, hypokalemia
B Fever, leukocytosis
C Rapid deep breathing, altered mental status, vomiting, polyuria[1]
D Polyuria, polydipsia, nocturia
3 Which of the following is not a known complication that can occur during management of DKA?
A Cerebral Edema
B Hypokalemia
C Pancreatitis
D Hematuria[1]
E Rhabdomyolysis
F Hypercholermic metabolic acidosis
G Mucormycosis
4 Which of the following explanations best explains the best initia[1] therapy for DKA after initial fluid resuscitation?
A Continuous IVF with 1/2NS or NS to replace fluid losses over 48 h, insulin gtt at 0.1 units/kg per hour[1]
B Continuous IVF with 1/2NS or NS to replace fluid losses over 48 h, insulin gtt at 0.05 units/kg per hour
C Maintenance IVF with 1/2NS or NS, insulin gtt at 0.1 units/kg per hour
D Maintenance IVF with 1/2NS or NS, IV insulin bolus followed by insulin gtt at 0.1 units/kg per hour
E Twice maintenance IVF with 1/2NS or NS, insulin gtt at 0.1 units/kg per hour
F Sodium bicarbonate administration, IV insulin bolus IV followed by insulin gtt at 0.1 units/kg per hour, maintenance fluids with 1/2NS or NS
5 What labs and how often should labs be drawn on a patient in DKA, including D-sticks?
A D-sticks Q1H, serum electrolytes Q4H
B D-sticks Q15 minutes, serum electrolytes Q2H
(1) D-sticks Q1H, serum electrolytes Q2H initially then Q4H once steady improvement is noted[1]
(2) D-sticks Q1H, serum electrolytes Q2H twice, then Q6H once steady improvement is noted
6 When should the patient's neurological status be assessed?
A On admission, every hour during treatment, as needed for acute changes[1]
B Every hour during treatment
C On admission, every hour for the first four hours of treatment and then as needed for acute changes
D On admission and as needed for acute changes
7 When should dextrose be added to your treatment of DKA?
A When blood sugar drops by more than 100 mg/dL in an hour
B When blood sugar is less than or equal to 250 mg/dL
C When blood sugar drops by more than 75 mg/dL in an hour
D When blood sugar is less than or equal to 300 mg/dL
E A and B
F A and D[1]
G C and D
H B and C
8 When should potassium not be added to the IVF?
A When potassium is < 5.5
B When patient has urinated
C When no EKG abnormalities are noted on cardiac monitor
D When patient has evidence of acute renal failure on lab evaluation[1]
9 Identify three signs/symptoms of cerebral edema
A Headache[1]
B Altered mental status[1]
C Hyperactivity
D Hypotension
E Bradycardia[1]
F Tachycardia
10 Over what period of time should you correct a patient in DKA's dehydration?
A Immediately
B Over 12 h
C Over 24 h
D Over 48 h[1]
E Over 72 h
11 When is the patient at the greatest risk for developing cerebral edema?
A On admission/before treatment
B At initiation of treatment
C Several hours into treatment[1]
D At the time of transition
12 Describe the process of how to transition a patient off an insulin drip onto SQ insulin (Do not need to describe calculating doses of insulin. Just the basic process)
A Order food tray, when food arrives, administer long acting insulin and mealtime SQ insulin, allow patient to eat, approximately one hour later discontinue the insulin gtt, and remove dextrose from fluids[1]
B Discontinue insulin gtt, administer long acting insulin when arrives
C Administer long acting SQ insulin, one hour later allow patient to eat and administer mealtime insulin, discontinue insulin gtt, remove dextrose from fluids
D Order food tray, when food arrives, allow patient to eat, administer long acting insulin and mealtime SQ insulin, approximately one hour later discontinue the insulin gtt
13 When should the insulin drip be stopped during the treatment of DKA?
A When the blood sugar drops by > 200 mg/dL
B During transport
C When the bicarb is 19
D When long acting SQ insulin has been given in consultation with endocrine[1]
14 Which of the following therapies is appropriate treatment of DKA?
A Bicarb administration
B Several hour delay or interruption in receiving insulin gtt
C Rapid drop in glucose during treatment
D Multiple fluid boluses at the beginning of treatment unless patient is hemodynamically unstable
E Starting the insulin drip one hour after IV fluid hydration has been initiated[1]

15 On a scale from 1 to 5, how beneficial did you find the simulation exercise?
1 2 3 4 5
Least helpful Most helpful
16 How would you improve this simulation exercise? (add this to the immediate post-test and not the one done at 3-6 mo)

[1]Correct answer.

than previous education on DKA. Residents echoed this positive response with all identifying the simulation as beneficial especially the interdisciplinary nature of the course.

Qualitative analysis found the following overall learning themes: (1) activity "felt like real life" by having the residents and nurses' work together; (2) longitudinal progression of events allowed learners to see a patient in different stages of treatment; (3) debriefing discussions regarding pathophysiology and linking it to treatment was helpful; and (4) early recognition of cerebral edema and management. Suggestions for improvement included: (1) utilize electronic order entry system; (2) provide written handouts; and (3) participate in the simulation earlier in training.

DISCUSSION

A multidisciplinary, longitudinal simulation can improve understanding of a medically complex disorder such as DKA. This is demonstrated by improvements in test scores from pre-simulation to initial post-simulation as well as when compared to the reference group. Certain aspects of DKA management including fluid administration and cerebral edema recognition showed sustained improvement. In an environment where patient exposure is often fragmented due to nursing shift schedules and duty hour restrictions, the longitudinal nature of this course allows participants to see a patient from initial diagnosis until transition to subcutaneous insulin. This aspect along with the multidisciplinary approach makes it unique amongst previously described studies[12-19].

Volkova *et al*[14] designed a multidisciplinary approach for implementation of DKA guidelines. Internal medicine residents were educated *via* computer based testing/supportive reading materials and separate nursing education was conducted through lectures/reading materials. Documentation of compliance to guidelines and knowledge assessments were performed on the residents. Improvement in both areas was noted. Our studied allowed for simultaneous learning analogous to patient care which added benefit in that healthcare professionals learn firsthand the complexities of effective communication when taking care of critically ill patients. Fung *et al*[15] conducted a systemic review regarding the use of interdisciplinary and interprofessional simulation as an education tool for crisis resource management. Specific gains including improvement in team communication and subsequently overall patient care were noted in three of the studies reviewed. Interprofessional simulation also provides a forum for learners to practice leadership roles in emergency situations. Brown *et al*[16] in 2014 demonstrated that a multidisciplinary simulation could be used to improve radiation oncology resident training for medical emergencies.

Few studies have looked specifically at simulation as a DKA educational tool. Schneider Sarver *et al*[17] developed a three part simulation involving management of an adolescent patient with mild, moderate, and severe DKA for nursing students which showed knowledge improvement. Lee Chin *et al*[18] compared high-fidelity simulation *vs* case-based learning modules for DKA and thyroid storm for senior pharmacy students. Both groups demonstrated knowledge improvements but the simulation group had higher post-test scores. Problem-based DKA simulation case series for medical students supplementing their basic science material or computer-based simulations as part of an outpatient endocrine rotation showed knowledge gains compared to traditional learning methods[19,20].

Our simulation course identified knowledge, communication and patient care gaps. For example, only half of residents completed a thorough neurological exam despite clinical evidence concerning for cerebral edema. When asked about this during debriefing, residents identified wanting to "rush" through the exam and not identifying a need to perform a more thorough exam. All nursing participants notified the resident physicians regarding the patient's clinical changes consistent with cerebral edema but only a few clearly communicated their concern was cerebral edema. Another example of communication breakdown was timing of insulin drip initiation in regards to fluid boluses and initiation of intravenous fluids. Sometimes fluid boluses and insulin drips were administered around the same time without clarification asked for by the nursing staff or provided by the prescribers. Per 2014 International Society for Pediatric and Adolescent Diabetes guidelines, delaying insulin drip initiation 1-2 h after beginning fluid resuscitation therapy can help decrease the risk of cerebral edema[4].

Knowledge decay over time has been reported as a concern in medical education literature[21,22]. In adult advanced life support training a recent review demonstrated that knowledge and skill decay can occur as quickly as six weeks after initial training with more significant decay noted at 6-12 mo which can be attenuated if subjects have more clinical topic exposure[21]. Doumouras *et al*[22] specifically discussed the use of simulation and retention of knowledge and skills for crisis resource management training and showed retention of skills, particularly team based skills, was maintained if a repeated intervention was utilized. These findings may help explain the lack of sustained knowledge improvement in our population. The exposure of our cohort to DKA patients between the conclusion of the simulation and the second post-test was not documented. Residents with more exposure to these

Table 2 Demographic Information for Control and Intervention Groups *n* (%)

Category	Control Group (*n* = 16)	Intervention Group (*n* = 20)	*P* value
Residency training year			0.003
PGY 2	0 (0)	8 (40)	
PGY 3/4	16 (100)	12 (60)	
Type of residency			0.192
Pediatric	13 (81)	19 (95)	
Medicine-pediatric	3 (19)	1 (5)	
Treated DKA in residency	16 (100)	20 (100)	0.192
Endocrine rotation only	2 (13)	4 (20)	
ICU rotation only	5 (31)	1 (5)	
Both endocrine and ICU rotation	6 (37)	9 (45)	
Other (ED, night float)	3 (19)	6 (30)	
Estimated number of patients treated with DKA			0.825
1-10	2 (13)	4 (20)	
10-20	8 (50)	9 (45)	
> 20	6 (37)	7 (35)	

PGY: Post graduate year; DKA: Diabetic ketoacidosis; ICU: Intensive care unit; ED: Emergency department.

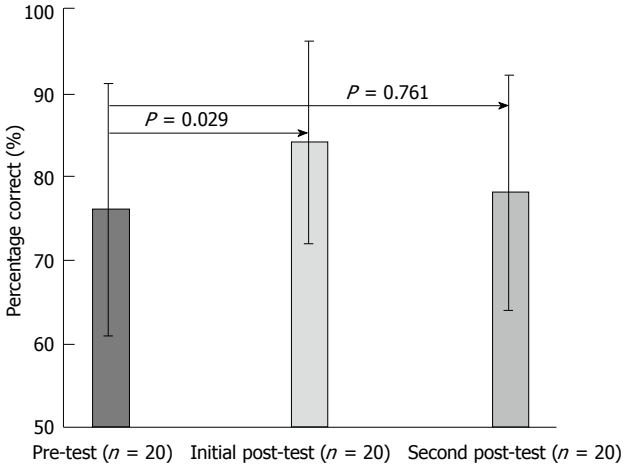


Figure 1 Assessment Scores for Intervention Group with standard deviation and respective *P* values.

patients to reinforce skills learned during the simulation may have performed better on the second post-test. Along those same lines, no structured reinforcement was offered between the conclusion of the simulation and the second post-test and this may have improved retention scores.

While our paper looks at the improvement of pediatric DKA management through simulation, we saw different methods utilized in each scenario. This difference in management of DKA in the pediatric population has been seen in other areas as well. Skitch and Valani[23] looked at the protocols of thirteen pediatric tertiary centers in Canada and reported many differences in the management of DKA. In comparison, a survey in pediatric centers in the Italian Society for Pediatric Diabetology and Endocrinology recognized significant differences in DKA management among their centers as well[24]. Both articles reference the need for evidence-based guidelines to be utilized across the board for best practice[23,24]. Although, DKA is managed through different methods, preventative care for these patients is of utmost importance. Crossen *et al*[25] concluded that signs of impending DKA were seen in children with type I diabetes who had recent emergency department visits and had infrequent subspecialty primary care visits. Chafe *et al*[26] utilized a focus study group of patients and families to identify ways to reduce episodes of DKA in the youth population. This project identified factors that put the youth at increased risks and recognized areas to improve those odds.

Limitations of this study included the relatively small number of participants especially in regards to numbers in the individual groups; reference, intervention and nurses. Recruitment of participants was limited due to the complex scheduling issues that are faced by both nursing staff and resident physicians. Other limitations include the reliance on participants to accept the realism in simulation activities. We chose to use a high-fidelity mannequin for the simulation to help reduce these issues. Each debriefing was designed to cover certain basic topics with all participants however may not have been identical. Finally, we did not assess if this intervention helped in actual care of patients with DKA.

Our study demonstrates that an interprofessional, longitudinal simulation improves short term understanding regarding the management of pediatric DKA. Subjectively, nurses found the interprofessional simulation improved their knowledge as well. It may be a useful tool to teach a team based approach and focus on communication between nursing staff and physicians when taking care of critically ill children. Unfortunately knowledge gains were not sustained at the 3-6 mo follow up sessions. Further studies are needed to investigate the impact of this simulation on patient care, specific changes in healthcare provider practices, and methods to reduce knowledge decay.

COMMENTS

Background

Diabetic ketoacidosis (DKA) is the most common pediatric endocrine emergency and understanding its management is important for the healthcare team. Experience and training in DKA management is variable and often separated by healthcare disciplines. Simulation may be an important tool to help standardize DKA training.

Research frontiers

Inter-disciplinary training with simulation is becoming an important way to train medical providers.

Innovations and breakthroughs

This is the first article to evaluate the role of inter-disciplinary simulation training in the management of pediatric DKA. Important knowledge gains were seen after the intervention but were not sustained on 3 mo follow-up.

Applications

Simulation is important tool in medical education and its role continues to

expand.

Peer-review

Nice research dealing with a public health problem.

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ORIGINAL ARTICLE

Retrospective Study

Determination of functional prognosis in hospitalized patients following an intensive care admission

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Augusto Motta University Centre.

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Abstract

AIM

To investigate the factors associated with the functional progress of hospitalized patients following an intensive care admission.

METHODS

Retrospective study including data from a cohort of 198 hospitalized patients following an intensive care admission and not requiring mechanical ventilation in a single tertiary referral hospital. A generalized linear model was used to identify the main effects of clinical and demographic variables on the outcomes of functionality (KATZ Index of Independence in Activities of Daily Living) and muscle strength (MRC Scale). The covariates identified as independent predictors were

analysed using the receiver operating characteristic curves. The analysis differentiated the periods in the intensive care unit (ICU), in the Ward (WARD) and the total time of hospital stay (TOT).

RESULTS

Considering the functional outcome (ΔKATZ), the variables that significantly contributed to the model (P < 0.05) were the KATZ and MRC on admission, age, sepsis (no), and total length of stay (TLS). Regarding the muscle strength outcome model (ΔMRC), the predictors were MRC on admission, Simplified Acute Physiology Score III, previous stroke, TLS, and sex (female). The variable age (AUC = 0.664) discriminated the $\Delta KATZ_{ICU}$. The variables age (AUC = 0.712), KATZ in ICU (AUC = 0.590) and on ward admission (AUC = 0.746), and MRC on ward admission (AUC = 0.721) were discriminative for $\Delta KATZ_{WARD}$. For $\Delta KATZ_{TOT}$ the variables KATZ on ICU admission (AUC = 0.621) and TLS (AUC = 0.617) were discriminative. For ΔMRC_{ICU} the variables SAPSIII (AUC = 0.661) and MRC on ICU admission (AUC = 0.653) were discriminative. MRC on ICU (AUC = 0.681) and ward admission (AUC = 0.553) were discriminative for ΔMRC_{WARD}. TLS (AUC = 0.649) and MRC on ward admission (AUC = 0.696) discriminative for the ΔMRC_{TOT}.

CONCLUSION

Specific functional, clinical and demographical variables at ICU admission are associated with the functional prognosis during the hospitalization period.

Key words: Muscle strength; Intensive care units; Activities of daily living; Rehabilitation; Early mobilization; Post-intensive care unit syndrome

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Core tip: In spite of the advances in critical care, functional deficits are commonly observed during and after the hospitalization period. This retrospective study aimed to investigate the factors associated with the functional progress in a cohort of patients that underwent a mobilization protocol, from the intensive care unit (ICU) to the hospital discharge. As functional ability, muscle strength, low illness severity score at ICU and ward admission, absence of sepsis and stroke, longer total length of stay, male gender and younger age were predictors of favourable patients' functional progress, these variables should be taken in consideration when planning rehabilitative strategies for hospitalized patients following an intensive care admission.

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INTRODUCTION

The advances in critical care have led to increased survival, however, physical and psychological deficits are commonly observed during and after the hospitalization period[1]. Intensive care unit acquired weakness (ICU-AW) is currently recognized as an important complication of critical illness. It is defined as symmetrical weakness in upper and lower limbs and is diagnosed with a medical research council (MRC) score sum less than 48[2]. Prolonged bed rest, systemic inflammation, hyperglycaemia, sedation, sepsis, malnutrition, patient immobilization, use of corticosteroids and neuromuscular blockers, among others, are considered risk factors for ICU-AW and, consequently, poorer functional outcome[3,4].

According to the World Health Organization International Classification of Functioning, Disability and Health[5,6], the key measures of physical function can be categorized as: (1) mobility: Including balance, lying, sitting, standing, shifting the body's centre of gravity; (2) muscle function: Strength; (3) walking and moving: Including walking independently, walking with assistance, walking short and long distances; (4) self-care: Activities of daily living (ADL) such as washing, dressing, toileting, grooming and eating; and (5) self-reported quality of life (QOL). Although 26 different functional instruments have been described for use in critically ill patients, proper assessment tools addressing impairment, activity limitations and participation restrictions need to be developed to be utilized across different time points of recovery[7]. The KATZ Index of Independence in Activities of Daily Living (KATZ ADL)[8] was first developed to assess the functional status in non-hospitalized older adults, and has been applied across a wide range of patient populations[9] and is one of the few functional scales that have been used both in critical care[10-12] and in the ward settings[11,13-15]. Similarly, the MRC, which was initially developed to assess the volitional muscle strength in outpatients[16], has been broadly used in critical care patients with a very good interrater reliability[17], however there are limitations to the use of volitional measures of muscle function in critically ill patients[18].

The literature however is still scarce concerning the factors that may determine the patients' functional recovery during the in-hospital period following a stay in intensive care. The ability to predict patient functional progress may contribute to the individualization of rehabilitative interventions. Additionally, the functional assessment throughout different time points of the in-hospital period, from the ICU admission/discharge to hospital discharge, using measures of muscle function and self-care may improve the understanding of the relationship between these two functional domains.

Thus, the primary objective of this study was to identify the factors that determine the functional progress of a cohort of patients that required an

intensive care admission without the need for mechanical ventilation and underwent a mobilization protocol, from the ICU admission to hospital discharge. Secondarily, we aimed at evaluate the association between the KATZ ADL index and the MRC scale during the same hospitalization period.

MATERIALS AND METHODS

Design

Retrospective study including data from a cohort of 198 hospitalized patients in a single tertiary referral hospital. The medical records from patients admitted to the ICU at the Barra D'Or Hospital between September 2013 and December 2014 were screened according to the eligibility criteria.

The generalized linear model was used to identify the main effects of clinical and demographic variables on the outcomes of functionality and muscle strength during the hospitalization period. The study was approved by the Institutional Research Board and Ethics Committee.

Participants

Data was obtained from non-mechanically ventilated patients presenting with at least one of the following criteria: KATZ score $\geqslant$ 3, MRC $\leqslant$ 48, diagnosis of pulmonary or cardiovascular disease, and cooperative (Richmond Agitation-Sedation Scale between 0 and 2) who stayed at least 48 h at the ICU and underwent the mobilization protocol. Records of patients who died during the period of the study, with neuromuscular disease, returned to the ICU after discharge or with incomplete data were not included.

Mobilization protocol and functional assessment

Eligibility criteria and procedures for the mobilization protocol followed the framework proposed by Hanekom *et al*[19] (2011). According to their clinical and functional condition, the patients progressed from passive and active mobilization and from being recumbent to ambulation as able. For patients unable to mobilize out of bed, lower limb strengthening exercises were included. Neuromuscular electrical stimulation and in-bed cycling exercises were not used. The interventions were undertaken daily on a twice a day basis.

The peripheral muscle strength was assessed by the MRC scale[16,17] which uses a 6-point scale from 0 (no contraction) to 5 (full contraction through range against resistance) of 12 muscle groups: Bilateral shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion. The representative score for each patient is the sum of the points given for each muscle group (maximum = 60).

The overall functional performance was assessed using the KATZ ADL index, which was culturally adapted for the Brazilian population[20]. This index assesses the subjects' ability to perform the following activities of daily living independently: Bathing, dressing, toileting, transferring, continence, and feeding. The scoring system gives a numerical score from "0" (independent in the six functions) to "6" (dependent in the six functions).

The mobilization protocol, muscle strength and functional performance were performed by the physical therapy team, who were periodically trained to ensure a these procedures were applied in a standardised way. The patients underwent the mobilization protocol from the ICU admission until the hospital discharge. Functional and muscle strength assessments were undertaken on three key periods: ICU admission, ICU discharge and hospital discharge.

Statistical analysis

Differences (delta, Δ) between the output and input values of hospital sectors were established as categorical outcomes ($\Delta SCORE_{period} = OUT_{score,period} - IN_{score,period}$). Such differences were calculated for periods of stay only in the ICU (ICU), only in the ward (WARD) and for the total hospital stay (TOT). Thus, considering that in the KATZ scoring system higher values are representative of poor functionality, the following categorization was set as $\Delta KATZ_{period} = 1$ if the sector's output score is lower than the input or $\Delta KATZ_{period} = 0$ if the sector's output score is higher or equal than the input. Conversely, considering that the MRC score is directly proportional to the functionality, the categorization was set as $\Delta MRC_{period} = 1$ if the sector's output score is greater than the input, $\Delta MRC_{period} = 0$ if the output score is equal or lower than the input.

Descriptive statistics included mean ± SD, median (minimum; maximum) or proportions for subjects aged < 65 years, $\geqslant$ 65 years, and the whole sample. Data between age groups were compared using independent-sample *t* tests for continuous variables, χ^2 test for categorical variables, and Fisher's exact test for dichotomous variables. Plots represent mean values alongside the 95%CI. Binary logistic, generalized linear model was used to identify the main effects of the factors (gender, "male" = 1; sepsis, "yes" = 1; COPD, "yes" = 1; dementia, "yes" = 1, previous stroke, "yes" = 1; and cause of ICU admission) and covariates (age; SAPSⅢ; length of stay; KATZ at admission; MRC at admission) on the outcomes of functionality and muscle strength ($\Delta KATZ_{period}$ and ΔMRC_{period}, respectively). The covariates identified as independent predictors were analysed using the receiver operating characteristic (ROC) curves. The value of state variable was coded "0" or "1", aiming to mirror the curve above the reference diagonal to facilitate the data interpretation. Cut-off points were determined by the minimal distance calculated as

$$d = \sqrt{(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2}$$ [21].

The association between MRC and KATZ scores was assessed through the Spearman's correlation coefficient, and all the results were considered significant when $P < 0.05$. All statistical analyses were performed with SPSS software (IBM Inc., United States).

Table 1 Subjects characteristics (n = 198)

Variables	Levels	Age < 65 yr	Age ≥ 65 yr	*P* value	All sample	
		Mean ± SD	Mean ± SD		Mean ± SD	Median (Min; max)
		n = 39	n = 159		n = 198	
Age, yr		50.5 ± 12.2	82.7 ± 8.6	NT	76.4 ± 15.9	80 (24; 101)
KATZ at ICU admission, score		3.9 ± 1.4	4.3 ± 1.4	0.207	4.2 ± 1.4	4 (0; 6)
MRC at ICU admission, score		46.6 ± 15.1	39.1 ± 14.9	0.007	40.6 ± 15.2	44 (0; 60)
KATZ at ward admission, score		2.7 ± 2.1	4.2 ± 1.6	< 0.001	3.9 ± 1.8	4 (0; 6)
MRC at ward admission, score		48.1 ± 15.0	40.0 ± 15.1	0.004	41.6 ± 15.3	45.5 (0; 60)
KATZ at hospital discharge, score		2.5 ± 2.2	4.0 ± 1.8	< 0.001	3.7 ± 2	4 (0; 6)
MRC at hospital discharge, score		50.6 ± 15.4	41.9 ± 14.0	0.002	43.6 ± 14.7	48 (0; 60)
Hospital length of stay, d		9.9 ± 7.0	12.1 ± 9.8	0.117	12 ± 9	9 (2; 52)
SAPS3, %		43.8 ± 8.8	53.7 ± 8.6	< 0.001	51.7 ± 9.5	51 (27; 89)
Gender, *n* (%)	Female	17 (14)	104 (86)	0.017	121 (61)	-
	Male	22 (29)	55 (71)	-	77 (39)	-
Sepsis, *n* (%)	No	19 (20)	74 (80)	0.859	93 (47)	-
	Yes	20 (19)	85 (81)	-	105 (53)	-
COPD, *n* (%)	No	37 (21)	142 (79)	0.377	179 (90)	-
	Yes	2 (11)	17 (89)	-	19 (10)	-
Dementia, *n* (%)	No	39 (27)	108 (73)	< 0.001	147 (74)	-
	Yes	0 (0)	51 (100)	-	51 (26)	-
Previous stroke, *n* (%)	No	38 (22)	134 (78)	0.032	172 (87)	-
	Yes	1 (4)	25 (96)	-	26 (13)	-
Cause of ICU admission, *n* (%)	Cardiovascular	4 (33)	8 (67)	0.646	12 (6)	-
	Gastrointestinal	3 (16)	16 (84)	-	19 (10)	-
	Neoplastic	0 (0)	1 (100)	-	1 (1)	-
	Neurologic	4 (25)	12 (75)	-	16 (8)	-
	Renal	8 (23)	27 (77)	-	35 (18)	-
	Pulmonary	16 (21)	62 (79)	-	78 (39)	-
	Others	4 (11)	33 (89)	-	37 (19)	-

KATZ: KATZ Index of Independence in Activities of Daily Living; MRC: Medical Research Council; SAPS3: Simplified acute physiology score; COPD: Chronic obstructive pulmonary disease; NT: Not tested.

RESULTS

A total of 198 subjects (121 females, 61%) aged 24 to 101 years (76.4 ± 15.9 years) were considered eligible for the study. From these, 78 were hospitalized for lung disease, 105 for sepsis, 19 had COPD, 51 had dementia and 26 had a prior stroke. The average length of hospital stay was 12 ± 9 d, and the average SAPSIII score was 51.7 ± 9.5 (Table 1). In the analysis of deltas for KATZ, 24.7% of the patients improved and 63.1% remained stable in $\Delta KATZ_{ICU}$, 23.7% improved and 66.7% remained stable in $\Delta KATZ_{WARD}$, and 36.4% improved and 51.5% remained stable in $\Delta KATZ_{TOT}$. For MRC, 28.8% improved and 57.1% remained stable in ΔMRC_{ICU}, 35.4% improved and 52.5% remained stable in ΔMRC_{WARD} and 47.0% showed improvement, and 35.4% remained stable in ΔMRC_{TOT}. The proportion of elderly patients (≥ 65 years) in the group was 80.3%. One hundred and thirty-four (67.7%) patients had a MRC < 48 at ICU discharge (consistent with the definition of ICU-AW), with only minimal improvement at hospital discharge with 122 (61.6%) with the MRC < 48. The functional and muscle strength progress through the different time points of the study are shown in Figure 1.

Considering the functional outcome during the ICU stay ($\Delta KATZ_{ICU}$), the variables that significantly contributed to the model were age (Wald χ^2 = 10.060, P = 0.002), KATZ at ICU admission (Wald χ^2 = 7.385, P = 0.007), MRC at ICU admission (Wald χ^2 = 4.837, P = 0.028) and previous stroke (Wald χ^2 = 4.671, P < 0.031). For the ward period ($\Delta KATZ_{WARD}$) the significant predictors were age (Wald χ^2 = 6.520, P = 0.011), KATZ at ward admission (Wald χ^2 = 12.782, P < 0.001), MRC at ward admission (Wald χ^2 = 4.418, P = 0.036), and sepsis (Wald χ^2 = 4.528, P = 0.033). Similarly, age (Wald χ^2 = 8.077, P = 0.004), total length of stay (Wald χ^2 = 6.629, P = 0.010) and KATZ at ward admission (Wald χ^2 = 10.099, P = 0.001) contributed for the functional outcome model considering the total length of stay ($\Delta KATZ_{TOT}$) (Table 2).

Regarding the muscle strength outcome during the ICU stay (ΔMRC_{ICU}), the SAPSIII (Wald χ^2 = 5.789, P = 0.016), MRC at ICU admission (Wald χ^2 = 9.645, P = 0.002) and previous stroke (Wald χ^2 = 8.815, P = 0.003) were significant predictors. For the ward period (ΔMRC_{WARD}) the predictors were the MRC at ICU admission (Wald χ^2 = 20.013, P < 0.001) and MRC at ward admission (Wald χ^2 = 12.085, P = 0.001). At hospital discharge (ΔMRC_{TOT}), the total length of stay (Wald χ^2 = 4.799, P = 0.028), MRC at ward admission (Wald χ^2 = 4.406, P = 0.036) and sex (Wald χ^2 = 3.864, P = 0.049) contributed for the model (Table 2).

Among the significant predictors in the generalized linear model analysed using the ROC curve, age (AUC = 0.664, cut-off = 78.5 years) was the only variable that discriminated the $\Delta KATZ_{ICU}$. For the ΔMRC_{ICU} the variables SAPSIII (AUC = 0.661, cut-off = 50.0%)

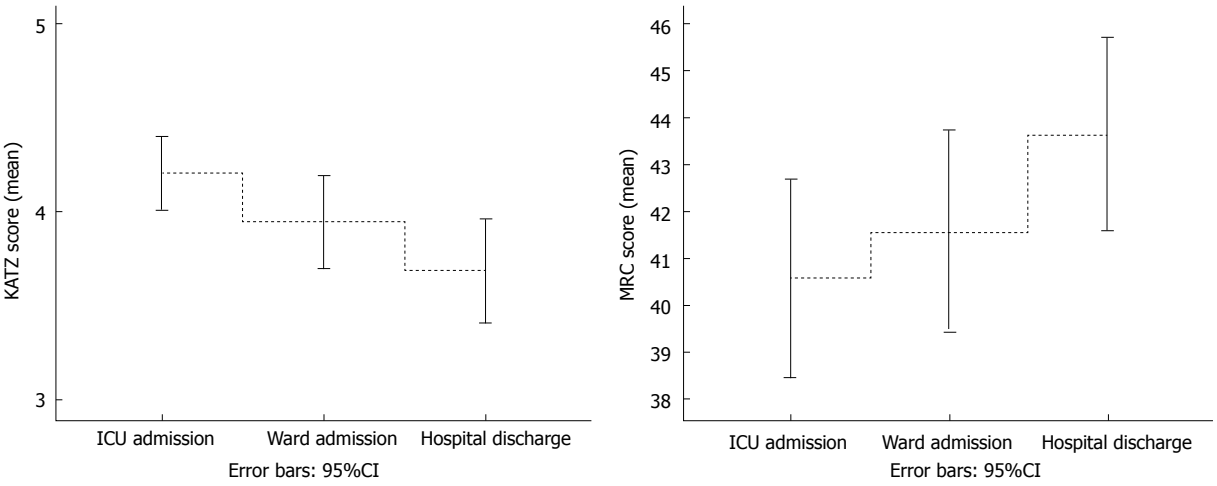


Figure 1 Functional progress through the different time points of the study. KATZ: KATZ Index of Independence in Activities of Daily Living; MRC: Medical Research Council Scale. Dashed lines represent step changes in mean values of scores between sequential time points of the study. ICU: Intensive care unit.

and MRC at ICU admission (AUC = 0.653, cut-off = 37 points) were discriminative. For $\Delta KATZ_{WARD}$, the variables of age (AUC = 0.712, cut-off = 81.5 years), KATZ at ICU admission (AUC = 0.590, cut-off = 4.5 points), KATZ at ward admission (AUC = 0.746, cut-off = 2.5 points), and MRC at ward admission (AUC = 0.721, cut-off = 47 points) were discriminative. The variables that significantly discriminated the ΔMRC_{WARD} were MRC at ICU admission (AUC = 0.681, cut-off = 44.5 points) and MRC at ward admission (AUC = 0.553, cut-off = 43.3 points). Finally, total length of stay (AUC = 0.617, cut-off = 11.5 d) and KATZ at ICU admission (AUC = 0.621, cut-off = 3.5 points) were the only variables that discriminated the $\Delta KATZ_{TOT}$. Whereas total length of stay (AUC = 0.649, cut-off = 10.5 d) and MRC at ward admission (AUC = 0.696, cut-off = 37 points) were the variables that significantly discriminated the ΔMRC_{TOT} (Figure 2 and Table 3).

There were weak significant associations between ΔMRC_{ICU} and $\Delta KATZ_{ICU}$ ($\rho = 0.264$; $P < 0.001$), ΔMRC_{ICU} and $\Delta KATZ_{WARD}$ ($\rho = 0.151$; $P = 0.034$) and ΔMRC_{TOT} and $\Delta KATZ_{TOT}$ ($\rho = 0.183$; $P = 0.010$).

DISCUSSION

Overall muscle strength and functional progress during hospitalization

The results of this study showed that, in spite of being cooperative and undergoing a mobilization protocol, only a small percentage of the patients in ICU improved their muscle strength (28.8%) and functional status (24.7%) in this setting. The same was observed in the ward period, with improvements in 35.4% of patients for muscle strength and 23.7% of patients for KATZ ADL index. This cohort of patients had low functional and muscle strength scores at hospital discharge, *i.e.,* KATZ = 3.7 and MRC = 43.6. Advanced age was identified as one of the determining factors of unfavourable functional progress in our study, and with the high prevalence of aged patients in our sample (80.3%, *i.e.,* 167 patients older than 65 years of age) this must have contributed to the poor functional progress during hospitalization and at hospital discharge. As shown in Table 1, elderly patients had more severe clinical condition at admission, as well as lower MRC scores and higher prevalence of previous stroke. Besides aging, these factors may have also contributed to the poorer functional scores observed on the ward and at hospital discharge in comparison with the younger subgroup.

Nevertheless, when considering the sample as a whole, there was a clear trend in improving MRC and KATZ scores throughout the hospitalization period (Figure 1). These results are in accordance with the study of van der Schaaf *et al*[22] (2009) who followed a sample of 255 participants during the ICU stay. In this study, even with a younger sample (mean age = 58.8 years), they found that 69% of the subjects had persistent limitations for the activities daily living even one year after the hospital discharge. In our study length of stay was a significant predictor of improvement in muscle strength and functional status when considering the total time of hospitalization. This suggests that the in-hospital functional and muscle strength recovery may be time-dependent. Hence[12] the extent of improvements in functional outcomes during hospitalization should be incorporated in hospital discharge planning. However, the evidence is still inconclusive regarding the benefits of exercise-based interventions on functional exercise capacity and health-related quality of life for survivors of critical illness[23]. Further research into the rehabilitation during hospitalization and post hospital discharge are required[24].

Predictors of muscle strength and functional improvement

A total of 134 (67.7%) and 122 (61.6%) of the patients presented with ICU-AW at ICU and hospital discharge, respectively. The high incidence of ICU-AW in this cohort of patients may be due to the high prevalence of sepsis

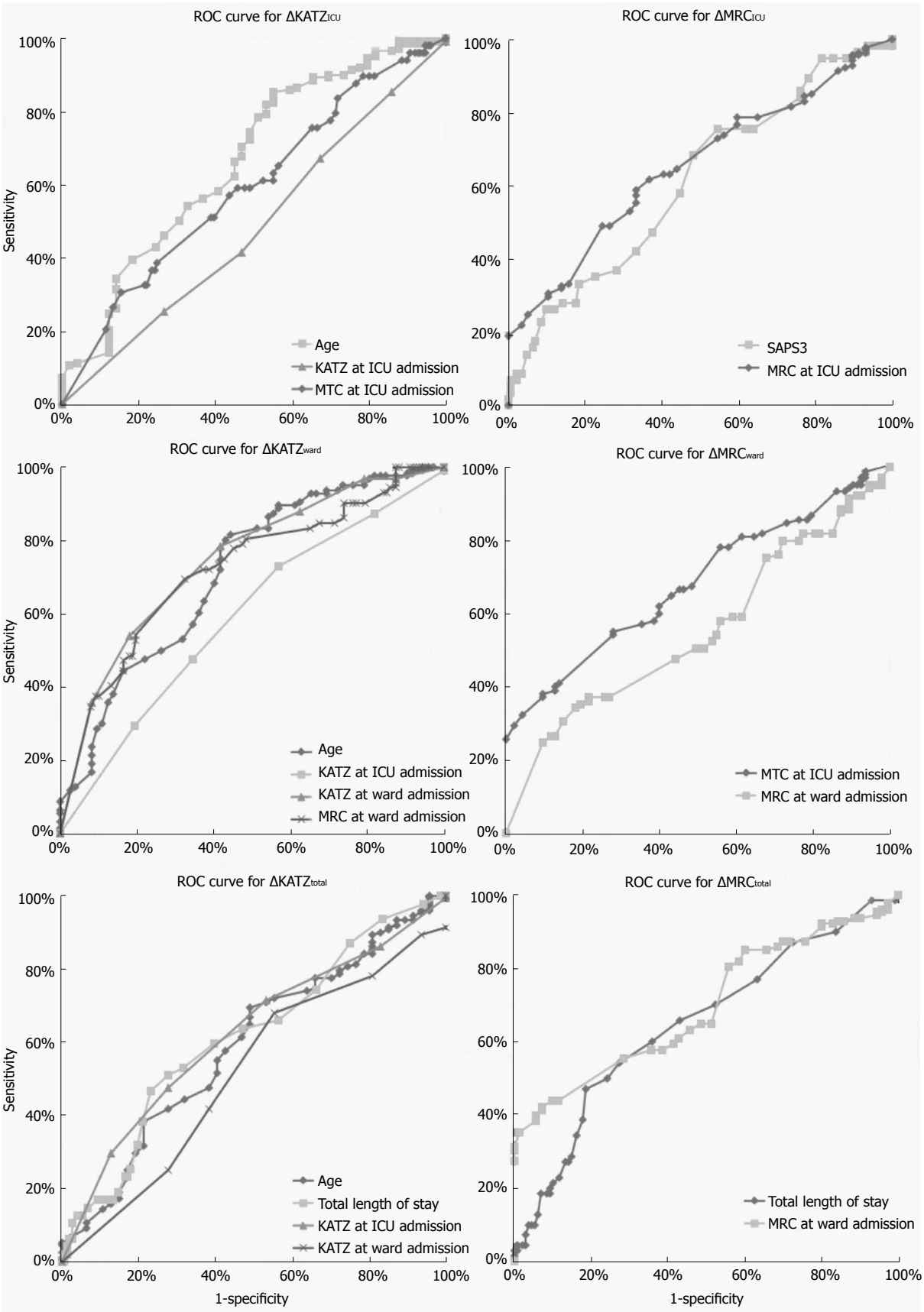


Figure 2 Receiver operator characteristics curves of improvement in KATZ ADL index (left panels) and MRC scores (right panels) during ICU stay (top panels), ward stay (center panels) and at hospital discharge (bottom panels). ΔKATZICU improvement of at least 1 point in the KATZ Index Score during the ICU stay; ΔMRCICU: Improvement of at least 1 point in the MRC Score during the ICU stay; ICU: Intensive care unit; KATZ ADL: KATZ Index of Independence in Activities of Daily Living; MRC: Medical research council.

Table 2 Generalized linear model results for functional outcomes (n = 198)

Functional outcome		ΔKATZ					ΔMRC				
		Test for model effects		Parameter estimates			Test for model effects		Parameter estimates		
Comparison	Variable	Wald χ^2	*P* (Sig.)	B	Lower 95%CI	Upper 95%CI	Wald χ^2	*P* (Sig.)	B	Lower 95%CI	Upper 95%CI
ICU	Age, yr	10.006	0.002	0.043	0.016	0.069	1.430	0.232	0.016	-0.010	0.042
	SAPS3, %	1.312	0.252	-0.023	-0.063	0.017	5.789	0.016	-0.053	-0.097	-0.010
	Length of stay in ICU, d	1.295	0.255	-0.040	-0.110	0.029	3.145	0.076	-0.068	-0.144	0.007
	KATZ at ICU admission, score	7.385	0.007	-0.562	-0.967	-0.157	0.399	0.528	0.119	-0.251	0.489
	MRC at ICU admission, score	4.837	0.028	-0.045	-0.084	-0.005	9.645	0.002	0.057	0.021	0.093
	Sex (male = 1)	0.069	0.792	-0.108	-0.913	0.697	0.733	0.392	0.341	-0.440	1.123
	Sepsis (no)	0.105	0.745	-0.133	-0.934	0.669	0.088	0.766	-0.122	-0.924	0.680
	COPD (no)	0.184	0.668	-0.302	-1.683	1.078	0.479	0.489	-0.488	-1.870	0.894
	Dementia (no)	0.238	0.626	-0.261	-1.312	0.789	1.478	0.224	-0.622	-1.626	0.381
	Previous stroke (no)	4.671	0.031	-1.782	-3.398	-0.166	8.815	0.003	-2.667	-4.428	-0.906
	Cause of ICU admission	3.785	0.706	NS	NS	NS	7.956	0.241	NS	NS	NS
Ward	Age, yr	6.520	0.011	0.040	0.009	0.071	1.235	0.267	0.016	-0.012	0.043
	SAPS3, %	0.137	0.711	0.008	-0.034	0.050	0.029	0.865	-0.004	-0.046	0.039
	Length of stay in ward, d	2.726	0.099	-0.047	-0.102	0.009	1.014	0.314	-0.028	-0.083	0.027
	KATZ at ICU admission, score	9.241	0.002	-0.858	-1.411	-0.305	1.185	0.276	0.228	-0.183	0.639
	MRC at ICU admission, score	1.339	0.247	0.034	-0.024	0.092	20.013	< 0.001	0.223	0.125	0.320
	KATZ at ward admission, score	12.782	< 0.001	0.867	0.392	1.342	0.503	0.478	0.123	-0.217	0.464
	MRC at ward admission, score	4.418	0.036	-0.064	-0.123	-0.004	12.085	0.001	-0.170	-0.265	-0.074
	Sex (male = 1)	0.548	0.459	0.306	-0.504	1.115	0.971	0.324	-0.361	-1.079	0.357
	Sepsis (no)	4.528	0.033	0.940	0.074	1.805	0.740	0.390	0.332	-0.424	1.087
	COPD (no)	0.035	0.852	-0.122	-1.404	1.160	1.978	0.160	0.881	-0.347	2.108
	Dementia (no)	0.138	0.710	-0.206	-1.290	0.879	0.063	0.803	0.120	-0.822	1.063
	Previous stroke (no)	0.362	0.548	-0.377	-1.606	0.852	0.067	0.796	-0.144	-1.231	0.943
	Cause of ICU admission	6.186	0.403	NS	NS	NS	4.222	0.647	NS	NS	NS
Total	Age, yr	8.077	0.004	1.465	-3.56	6.490	0.243	0.622	0.007	-0.019	0.033
	SAPS3, %	0.816	0.366	0.044	0.014	0.075	0.832	0.362	0.019	-0.021	0.059
	Total length of stay, d	6.629	0.010	-0.021	-0.066	0.024	4.799	0.028	-0.039	-0.075	-0.004
	KATZ at ICU admission, score	10.269	0.001	-0.056	-0.098	-0.013	0.024	0.876	-0.031	-0.424	0.362
	MRC at ICU admission, score	0.257	0.612	0.826	0.321	1.331	1.077	0.299	-0.024	-0.069	0.021
	KATZ at ward admission, score	10.099	0.001	0.014	-0.040	0.069	0.006	0.937	-0.014	-0.364	0.336
	MRC at ward admission, score	2.743	0.098	-0.752	-1.215	-0.288	4.406	0.036	0.049	0.003	0.095
	Sex (male = 1)	0.157	0.692	-0.047	-0.102	0.009	3.864	0.049	-0.751	-1.499	-0.002
	Sepsis (no)	1.589	0.208	0.169	-0.668	1.007	0.439	0.508	0.247	-0.484	0.978
	COPD (no)	0.002	0.968	0.594	-0.330	1.517	1.076	0.300	0.570	-0.507	1.648
	Dementia (no)	0.028	0.866	-0.026	-1.318	1.265	0.629	0.428	-0.363	-1.261	0.534
	Previous stroke (no)	0.046	0.831	-0.097	-1.226	1.032	3.273	0.070	0.911	-0.076	1.899
	Cause of ICU admission	12.048	0.061	NS	NS	NS	2.985	0.811	NS	NS	NS

KATZ: KATZ Index of Independence in Activities of Daily Living; SAPS3: Simplified acute physiology score; MRC: Medical Research Council; COPD: Chronic obstructive pulmonary disease; NS: No significant; A: Significant differences for categories cardiovascular and respiratory; B: Significant differences for categories gastrointestinal and respiratory.

Table 3 Receiver-operating characteristic curve analysis for significant factors for predicting functional outcomes

Functional outcomes		ΔKATZ					ΔMRC				
		AUC	Cut-off	Sensitivity	Specificity	*P* (Sig.)	AUC	Cut-off	Sensitivity	Specificity	*P* (Sig.)
ICU	Age, yr	0.664	78.5	41%	42%	0.001	[1]	[1]	[1]	[1]	[1]
	SAPS3, %	[1]	[1]	[1]	[1]	[1]	0.661	50.5	68%	52%	0.014
	KATZ at ICU admission, score	0.515	4.5	47%	58%	0.753	[1]	[1]	[1]	[1]	[1]
	MRC at ICU admission, score	0.592	45.5	57%	56%	0.053	0.653	37	44%	35%	0.001
Ward	Age, yr	0.712	81.5	32%	47%	< 0.001	[1]	[1]	[1]	[1]	[1]
	KATZ at ICU admission, score	0.590	4.5	35%	52%	0.035	[1]	[1]	[1]	[1]	[1]
	MRC at ICU admission, score	[1]	[1]	[1]	[1]	[1]	0.681	44.5	39%	42%	< 0.001
	KATZ at ward admission, score	0.746	2.5	63%	12%	< 0.001	[1]	[1]	[1]	[1]	1
	MRC at ward admission, score	0.721	47	69%	67%	< 0.001	0.553	43.3	54%	48%	0.200
Total	Age, yr	0.592	81.5	38%	52%	0.058	[1]	[1]	[1]	[1]	[1]
	Total length of stay, d	0.617	11.5	51%	72%	0.016	0.649	10.5	54%	73%	0.001
	KATZ at ICU admission, score	0.621	3.5	53%	28%	0.012	[1]	[1]	[1]	[1]	[1]
	KATZ at ward admission, score	0.515	4.5	38%	58%	0.750	[1]	[1]	[1]	[1]	[1]
	MRC at ward admission, score	[1]	[1]	[1]	[1]	[1]	0.696	37	51%	35%	< 0.001

[1]Variables with no significant effect on the generalized linear model were not analyzed using ROC curves. KATZ: KATZ Index of Independence in Activities of Daily Living; MRC: Medical Research Council; SAPS3: Simplified acute physiology score; AUC: Area under the curve.

(53%) and increased age in our sample[25,26].

Nonetheless, higher MRC scores at ICU admission were predictive for the improvement in muscle strength and functionality during the ICU stay. These results reinforce the concept that more attention by physical therapists should be given to patients with reduced muscle strength at ICU admission. In this way, the early application of rehabilitation may benefit selected patients. Specifically the application of electrical muscle stimulation[27] or in-bed cycling[28] in the patient group who are un-cooperative or with very poor muscle strength may be beneficial but requires more prospective evaluation.

Interestingly, the KATZ indexes at ICU admission were predictive only for the functional improvement. As a minimum degree of muscle strength is needed for performing the self-care activities, it is likely that individuals with higher KATZ scores had strength about 4-5 in the muscles assessed by the MRC scale. Thus, due to the ceiling effect, further improvements in muscle strength were not detected in patients with higher KATZ scores.

Surprisingly, dementia, considered an exclusion criterion in some mobilization trials 1[11] was not a predictor of no-improvement in muscle strength. Conversely, previous stroke, which results in variable degrees of neuromuscular disability, was predictive of non-improvements in KATZ and MRC scores during the ICU stay.

Functional assessment

The functional progression of hospitalized patients is dependent on many factors. For example, nutritional status, use of certain drugs (corticosteroids, neuromuscular blockers, *etc.*), hyperglycaemia, and multiple organ failure[3,29,30], among others might have influenced the results of this research. Although it can be considered a limitation, we used a representative sample of critically ill patients, and our outcomes provided functional, demographic and clinical parameters to be used as general predictors of muscle strength and functional progress during the hospitalization period. We believe that the findings of this study add new relevant information for the early rehabilitation and mobilization protocols, as well as to serve as a starting point for further research on the individual factors to be considered for these types of intervention.

The functional assessment instrument used in this study was not originally developed for use in the intensive care unit. Similarly, other functional instruments designed for outpatients, such as the Barthel Index and the functional independence measure (FIM) have been used in intensive care[6]. As many ICU patients may present with a very low functional capacity, it is likely that these general functional instruments have some limitation concerning their clinimetric properties. For example in ICU there may be potential for a floor or ceiling effect; limited ability to detect meaningful change (responsiveness) and/or minimal clinically important difference[7]. To date there are no instruments designed to follow the functional progress of patients' from ICU admission to hospital discharge and beyond. Therefore, such general scales seem to be useful for the long term prospective functional monitoring, for both clinical and research purposes.

As intubated and mechanically ventilated patients were not included in this study, it was not possible to analyse the influence of this factor on muscle strength and functional progress during hospitalization. Although muscle weakness is associated with prolonged weaning from mechanical ventilation, there is large variability in the reported prevalence of ICU-AW among mechanically ventilated patients[31]. Therefore, future studies should address if mechanical ventilation is an independent predictor of peripheral muscle strength and functional progress in critically ill patients. Another limitation of the study is that data from deceased patients were not included and analysed. As we used secondary records and patients with incomplete data were excluded, this information was not available in our database. Our study did not focus on mortality outcomes and it hence it would not have been possible to analyze functional progress of these subjects throughout all time points.

In conclusion, better functional patient condition and low severity of illness score at ICU admission, absence of sepsis and stroke, longer total length of stay and age lower than 78.5 years are predictors of favourable patient functional progress during hospitalization following an intensive care admission.

COMMENTS

Background

The advances in critical care have led to increased patient survival, however, severe deficits in physical and psychological status are commonly observed during and after the hospitalization period. The possibility of predicting the patients' functional progress may assist to contribute to individualized rehabilitative interventions in this cohort of patients'. The authors investigated the determining factors of functional progress in a cohort of patients that required intensive care unit (ICU) admission without mechanical ventilation that underwent a mobilization protocol, from the ICU to hospital discharge.

Research frontiers

It un-clear which factors influence the patients' functional recovery during the in-hospital period after a stay in ICU. This study identifies the clinical and functional characteristics that influence the functional progress of hospitalized patients.

Innovations and breakthroughs

These results demonstrated a high prevalence of Intensive Care Unit Acquired Weakness and functional impairments at hospital discharge, similar to previous research. The authors have defined key clinical and functional parameters that predict the functional progress of hospitalized patients who underwent a standardized mobilization protocol through the ICU and the ward setting.

Applications

The rehabilitation of hospitalized patients who require an ICU admission without mechanical ventilation should take into account the predictors of poor functional outcomes identified in this study.

Peer-review

This is a well-written manuscript about functional rehabilitation and muscle strength following an ICU admission.

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ORIGINAL ARTICLE

Prospective Study

Early debridement and delayed primary vascularized cover in forearm electrical burns: A prospective study

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Informed consent statement: All study participants, or their legal guardian were explained in their own language about the inclusion in the study. Informed written consent was duly taken prior to enrollment in the study.

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Abstract

AIM

To look into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue in electrical burns.

METHODS

A total of 16 consecutive patients sustaining full thickness forearm burns over a period of one year were included in the study group. Debridement was undertaken within 48 h in 13 patients. Three patients were taken for debridement after 48 h. Debridement was repeated within 2-4 d after daily wound assessment and need for further debridement.

RESULTS

On an average two debridements (range 1-4) was required in our patients for the wound to be ready for definitive cover. Interval between each debridement ranged from 2-18 d. Fourteen patients were provided vascularized cover after final debridement (6 free flaps, 8 pedicled flaps). Functional assessment of gross hand function done at 6 wk, 2 mo, 3 mo and 6 mo follow-up.

CONCLUSION

High-tension electrical burns lead to significant morbi-

dity. These injuries are best managed by early decompression followed by multiple serial debridements. The ideal timing of free flap coverage needs further investigation.

Key words: Early debridement; Vascularized cover; Electrical burns; Forearm

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Core tip: High-voltage electrical injuries lead to be a significant morbidity associated with severe socioeconomic implications. There is conflicting evidence in the literature regarding progressive tissue necrosis in this devastating injury. We looked into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue, which can potentially prevent further progression of this pathology. We found that the phenomenon of ongoing necrosis was not halted in our study and all our early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma. Electrical injuries were progressive in nature and required multiple radical debridement until the wound is ready for definitive cover.

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INTRODUCTION

Contact electrical injuries are a cause of significant damage to tissues, which often result in amputations to the extremities. Unlike the damage caused by thermal burns, high-voltage electrical burns tend to cause a severe and complex injury pattern. There can also be associated neurologic, cardiac, renal, gastrointestinal, ophthalmologic, and psychiatric disturbances[1]. Thus, electrical burns are associated with a significant morbidity, including high amputation rate which in turn is a cause of higher socioeconomic implications[2]. In a study by Noble *et al*[1], 45% of patients with electrical burns needed to change their profession and 32% were not able to return to work. Majority of the high voltage electrical injuries occur at the workplace in the adult age group. In children, injury is usually accidental occurring while playing near high voltage power supply lines[3].

The vascular endothelium provides a high resistant to the flow of electrical current; therefore, the damage was more significant along inner vascular wall. Initially, large blood vessels may appear patent, but if the endothelium was damaged mural thrombi would form, resulting in thrombosis and distal limb ischemia[4]. Thus, considering the conflicting evidence in the literature regarding progressive tissue necrosis, and high amputation rates of this devastating injury, we looked into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue, which was hypothesized to prevent further progression of this pathology.

MATERIALS AND METHODS

This was a prospective study which was conducted over a period of 12 mo in the Department of Plastic Surgery at a tertiary level teaching hospital, to include all patients of electrical forearm burns. Those patients with associated life threatening injuries, or obviously charred limb at the time of presentation were excluded. Over a period of 1 year, 81 patients presented with history of sustaining electrical burns. Among these forty-two patients (51.85%) sustained injury to forearm, with or without involvement of other parts of body. However in 18 patients (42.8%) the limb was charred following contact and were excluded. Three (6.9%) patients with severe head injury and 5 (11.9%) patients with spinal cord injury resulting in paraplegia were excluded from the study. Thus, out of total 81 patients, 16 patients fulfilled the inclusion criteria and were included in the study. Patients presenting within 48-96 h were assessed for depth of tissue involved, both clinically and with PET findings. Those presenting later than 96 h were assessed for tissue involvement during debridement.

All patients sustaining these injuries were males and the mean age was 26 years. All injuries were due to high voltage electric contact over hand and forearm. Those presenting within 48 h (n = 6) were infused with Lactated Ringer's infusion with monitoring of urine output, ECG monitoring, and circulatory assessment at 1 hourly intervals as per standard burn resuscitation protocols. Baseline investigations were done on admission and were monitored daily for 7 d. Assessment of urine for myoglobin and renal parameters were done on admission and repeated everyday if deranged. ECG was performed at admission to rule out cardiac irregularities and to assess for hyperkalemia. Those with deranged renal function (n = 2, 12.5%) were assessed and managed in collaboration with nephrologist.

The area of burn was examined and dimensions measured from bony landmarks. The graphical tracing of the injured area was used to measure the length and breadth of the wound while depth of involvement was assessed mainly by identifying structures involved during debridement. Distal limb viability was assessed by examining presence or absence of distal pulsations, capillary refill time and pulse oximetry readings compared with opposite healthy limb if uninjured. In the presence of compromise in the circulation, subjective neurosensory disturbance, pain with passive stretch of intrinsic musculature, decrease in oximetry readings to affected digits or extremity, liberal fasciotomy



Figure 1 Electrical burns involving volar forearm.

was done with standard defined incisions to release the compartment pressure. Circulatory status was examined and noted at 4 hourly intervals for 24 h and 8 hourly thereafter for 4 d.

Of 16 patients in the study group only 4 patients presented within 96 h and were assessed with PET FDG scan for the depth of tissue involvement. The scan was performed using a Discovery STE-16 PET-CT scanner (GE Healthcare, Milwaukee, United States) after intravenous injection of 370-444 MBq (10-12 mCi) of F-18 FDG. Debridement was undertaken within 48 h in 13 patients. The presence of obvious necrosis was indication for necrectomy. Three patients were taken for debridement after 48 h. One out of 3 had only fasciotomy wound with viable muscles clinically. On primary wound assessment in 2 patients, muscles were not obviously necrotic and were reassessed before debridement. Procedure was conducted under regional or general anesthesia, using tourniquet in all cases. Extent of involvement of muscles, tendons, nerves and vessels were noted. Bleeding, colour and contractility of muscles, along with status of tendons nerves and vessels were noted after tourniquet release.

Debridement was repeated within 2-4 d after daily wound assessment and need for further debridement. On an average two debridements (range 1-4) was required in our patients for the wound to be ready for definitive cover. Interval between each debridements ranged from 2-18 d.

Flap cover was planned depending upon status of the wound. Distant pedicled flaps and free flaps were used to resurface these defects. Locoregional flaps were not available for use due to the nature of the injuries. A total of 8 distant pedicled and 6 free flaps were undertaken. The functional and aesthetic outcome was assessed at 6 wk, 2 mo, 3 mo and 6 mo follow-up. Clinical assessment was done for median, ulnar, and radial nerves, and touch sensations at respective nerve territory were noted. ROM both active and passive of all joints of hand was documented. Patients were provided with activities of daily living (ADL) charts at 3 mo follow-up and asked to score depending on the scale of easy to difficulty in performing outlined tasks. These were scored as 1-no difficulty in performing the activity, 2-mild difficulty, 3-moderate difficulty, 4-severe difficulty, 5-cannot do at all. These activities were reassessed at 6 mo follow-up and any improvement or change of score was noted.

The statistical methods used in this study were approved in ethics committee/institute review board which has biostatistician as a co-opted member.

RESULTS

A total of 16 patients satisfied the inclusion criteria and constituted the study group. Patient's age ranged from 10-45 years, average age being 26 years. All of these 16 patients were males. Incidence of electrical injuries during work was 81.25%. Ten patients were farmers working at the field near transformers, three were electricians injured while repairing high voltage lines. The three pediatric age group patients had contact with high-tension cables running nearby, while playing or flying kite.

All patients were right handed and all injuries were due to high voltage. The dominant hand was affected in 12 of the 16 patients. Bilateral limbs were involved in seven patients Seven (7/16 - 44%) patients required fasciotomy. Fasciotomy was done under local anesthesia in emergency room with standard defined incisions to release the compartment pressure. Of 16 patients, derangement of renal function was observed in two patients (12.5%). One patient required multiple sittings of haemodialysis and other patient was managed conservatively with forced diuresis and urine alkalinization. On assessment of wound prior to debridement the average surface area involved was found to be 40.37 cm^2 (range 5-82.5 cm^2). The volar forearm was involved in 14 patients; while 2 patients had involvement of hand, and thumb (Figure 1). The hand as a whole was viable in all patients, except two patients who had non-viable little finger which required debridement. Patients had involvement of either median, ulnar nerve. Radial nerve was not involved as injury was predominantly on volar aspect of forearm. Three patients showed involvement of combined median and ulnar nerve. Involvement of only median nerve was seen in two patients, while only ulnar nerve was involved in six patients.

PET scan was done in four patients for assessment



Figure 2 Forearm electrical burns after multiple debridements.



Figure 3 Final outcome after flap cover.

of involvement of deeper tissues focusing on accuracy and predictability of PET in assessing this. FDG uptake was adequately seen in upper third proximal muscle bellies of volar forearm. Pronater quadratus was involved in three cases, *i.e.*, showed no glucose uptake. Flexor digitorum profundus was involved in all four patients. Flexor digitorum superficialis was injured in three-patients. The debridement findings in these patients correlated well with PET findings.

Debridement was undertaken under regional or general anesthesia, tourniquet was used in all cases. Debridement was considered to be complete when clinically there was no evidence of obvious necrotic tissues or slough in the wound (Figure 2). Patients underwent regular dressings and removal of obvious necrotic tissues during dressings. Debridement was repeated under anesthesia and tourniquet control in 10 patients and in six patients single debridement was done. Seven patients with bilateral limb involvement required more than one debridement, range 2-4 (mean 3 debridements). Three patients with unilateral limb involvement required more than one debridement (mean 2). The mean surface area of the wound after final debridement was measured 47 cm^2 (range 5-96 cm^2) from initial measurement of 40.37 cm^2 showing 15.9% increase. Fourteen patients were provided vascularized cover after final debridement (6 free flaps, 8 pedicled flaps) (Figure 3); two patients had viable muscles exposed post fasciotomy, which were covered with skin graft.

Free flaps were selected on the basis of size and shape of wound, tissue requirement, availability of the recipient vessels and general condition of patient. Distant pedicled flap was selected in cases with recipient vessels involvement, associated proximal injury leading to impaired venous return of distal part, and associated co morbidities. Of the 6 free flaps, anterolateral thigh flap (n-2), latissimus dorsi flap (n-1), thoracodorsal artery perforator flap (n-2), and lateral arm flap (n-1) were done. In four patients, ulnar artery was used as a recipient vessel, while in two patients radial artery was used as a recipient vessel. Three out of six free flaps necrosed. All patients in whom flaps failed had undergone single debridement before flap transfer. The status of wound prior to flap transfer in these three patients showed apparently healthy looking and viable muscles. The vessels including radial and ulnar artery were patent proximally. All three flaps were transferred between 2-8 d post injury. Earliest free flap was done 2 d after debridement in which flap necrosed. Three flaps, which survived, were transferred after two weeks of injury. In case of distant pedicled flaps, 2 groin flaps, 1 bipedicled abdominal flap, 5 thoraco-umbilical flaps were used.

Functional assessment of gross hand function done at 6 wk, 2 mo, 3 mo and 6 mo follow-up. Patients were provided with ADL charts and asked to score depending on the scale of easy to difficulty in performing outlined tasks. The ADL score in all 16 patients were between 3-5. There was no progression and/or improvements in scores at three and six months follow-up.

DISCUSSION

The aims of treatment in electrical burns are to achieve good final function with good cosmetic appearance along with early return to a normal productive life. The aim of present study was to assess whether the extent of forearm injury and tissue damage was progressive and to determine whether early debridement and

vascularized cover prevented progressive tissue necrosis and halted further progression.

Electrical injury usually affects young age group individuals; the incidence is high amongst males as compared to females because of work related nature of injury. The age group involved in various studies ranged from 10-50 years[5-7]. In our study, we observed 81.25% of the injuries to occur during work. Majority of our patients were farmers injured while working in the fields near transformers. We also observed a clear relationship between hand dominance and limb involved as 75% of our patients had dominant limb affected by injury supporting the observation that most of injuries occurred at workplace.

There is a significant variation in the rate of escharotomy/fasciotomy in electrical burns, which ranges from 9.2% to 54%[1,4,5]. Although, some studies advocate an immediate decompression[8], this concept has been questioned by others[9]. Mann *et al*[9] advocated selective decompression only in the presence of signs of compartment syndrome. They have based their algorithm on a continuous clinical evaluation and they opine that selective, non-immediate decompression may preserve tissue thus contributing to lower amputation rates. They did fasciotomy in 22% of their patients within 24 h. We opted for decompressive fasciotomy within 48 h of injury in 56% of patients.

d'Amato *et al*[3] and Ferreiro *et al*[5] in their individual studies supported the fact of early and radical debridement of all the necrotic tissues in electrical burns. d'Amato *et al*[3] also suggested the value of extended fasciotomy to access the viability of muscles. They said debride when necessary, and relieve the pathologic elevation of compartment pressures in an attempt to prevent ongoing neuromuscular damage. These observations support the need of early exploration with wide exposure of deep muscle compartments to assess the extent of injury in high-voltage burns. In present study, we did fasciotomy in nine patients with signs of increased compartment pressure and found that neuromuscular damage could be prevented with extended fasciotomies.

Scheker *et al*[8] were also of opinion that a wound should be radically debrided and cover should be provided immediately, they have proven this method of treatment to be superior to conservative debridement and delayed vascularized cover. They concluded that immediate reconstruction of severe upper extremity injuries is associated with increased function, lesser complications and a shorter hospital stay. According to authors, immediate reconstruction also permits earlier mobilization thereby preventing the tendon adhesions. We opted for radical debridement in our patients; however, the ongoing progression of tissue necrosis prevented us from immediate reconstruction.

García-Sánchez *et al*[2] observed myoglobinuria in 70% of their patients, while Mann *et al*[9] had reported 53.2% patients had myoglobinuria. In neither of these studies, authors observed their patients requiring haemodialysis for renal failure. Ferreiro *et al*[5] required hemodialysis in 3% of their patients. We observed two patients with myoglobinuria, one of which required haemodialysis. Both patients showed improvement in their renal functions after debridement. Thus, we observed that low urine output, and persistent acidosis is indication for exploration and debridement rather than conservative management of myoglobinuria.

Ferreiro *et al*[5] reported that the most frequently affected nerves were the ulnar and the median nerves. In their series, the incidence of peripheral neurological injury was 30%. The permanent peripheral neurological injury was located at the point of entry of the current in 88% of the cases and there was no recovery of sensations or movement during a period of six months after the trauma. Mazzetto-Betti *et al*[7] had ulnar clawing in 22% and median claw in 5% of cases. Analyzing hand sensation in their study, the radial nerve was the least affected among the patients. Sensation improvement was worst for the median nerve. In present study, we observed 38% patients with injury to ulnar nerve, while median nerve was affected in 12.5% of patients. Combined median and ulnar nerve was seen in 19% patients while none of our patients had involvement of radial nerve because of predominant involvement of volar forearm in our patients.

Burn wound depth is a significant determinant of patient treatment and morbidity. Devgan *et al*[10] reviewed modalities for the assessment of burn wound depth and concluded that Indo cyanine green video angiography or Laser Doppler Imaging is appropriate to best assess the depth of acute burn wounds. Nettelblad *et al*[11] used MRI as diagnostic modality in two patients with electrical burns. They suggested that the alteration of tissue signal exhibited by necrosed muscle is not specific to the injury mechanism. Smith *et al*[12] investigated the use of 18FDG PET scanning for assessment of skeletal muscle viability. They concluded that FDG-PET scanning could determine skeletal muscle viability in patients with peripheral vascular disease and in patients following free-flap transfer. In our study, we used FDG PET for assessment of muscle viability in four patients who presented within 96 h of injury. The numbers were less because of varied timing of presentation of patients. The findings at debridement correlated well with PET findings and the investigation aided the surgeon during debridement. The tool can be used in conjunction with clinical evaluation for deep muscle necrosis in electrical burns but further studies are needed in this context to reach any definitive conclusion.

The distant microvascular tissue transfer primarily aims at improving limb salvage rates in electrical burns. The transfer of well vascularized distant tissue in an ischemic bed can potentially lead to preservation of tissues. However, the best timing for free microvascular tissue transfer in electrical burn injuries remains debatable. Sauerbier *et al*[13] reported a higher free flap failure rate of 24% in electrical burns during primary

reconstruction (within 5-21 d after trauma). In their later publication, they described a "vulnerable phase" of 3 wk after trauma in which vascular instability may compromise free flap success[14]. In contrast to this finding, Koul *et al*[15] found no variation in flap survival when performing microvascular tissue transfer in this vulnerable phase. Similar findings were reported earlier by Ninkovic *et al*[16]. Our own results favor the hypothesis of a vulnerable phase. In our series, flap failure due to microvascular thrombosis was seen exclusively in flaps transferred during the first 2 weeks. In our study, we found that the injury was progressive in nature and eventually required multiple radical debridements until the wound was ready for definitive cover. The phenomenon of ongoing necrosis was not found to be halted in our study and all our early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma. Shen *et al*[17] also observed the phenomenon of distal flap necrosis and wound bed necrosis in early coverage of forearm electrical burns. Dega *et al*[18] were also able to achieve stable wound bed in patients of electrical burns after 12 d.

In present study, we observed average 61 d of hospital stay, which was directly related to number of procedures patient required for definitive wound cover. Handschin *et al*[19] reported average 44 d of hospital stay and Noble *et al*[1] in their study reported hospital stay 24.5 ± 21 d in electrical injuries.

The return to work data in the existing literature is rare and is difficult to interpret. A retrospective review by Mazzetto-Betti *et al*[7] reports that 72% patients retired or changed their job. Kidd *et al*[6] however reported that average time to return to work was 101 d post injury. Six patients in our study, returned to work after average 98 d post injury. Amongst these, three were students, two were farmers, and they adapted to use their contra-lateral uninjured limb. One patient was electrician who changed his job and presently doing farming with uninjured limb. None of our patients with bilateral involvement returned to work.

Following analysis of 16 patients of forearm electrical burns, it was concluded from the study that: (1) most common victims of electrical injury were young adult males. It affected the dominant limb more commonly and injury predominantly occurred at the workplace; (2) fasciotomy performed within 48 h of injury with slightest evidence of compartment syndrome was found to be limb saving; (3) there was a direct correlation between the point of entry of the current and the resulting neurological injury; (4) the clinical and PET assessment of deeper soft tissue involvement showed that injury affected periosseus tissues more than superficial muscles and skin; (5) electrical injuries were progressive in nature and required multiple radical debridement until the wound is ready for definitive cover; (6) the phenomenon of ongoing necrosis was not halted in our study and all our early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma; and (7) distant pedicled flaps offered a viable and safe option for early coverage of hand and forearm defect in the presence of recipient vessel injury. To conclude, high-tension electrical burns represent a severe injury with significant morbidity and the time tested concepts of early fasciotomy followed by repeated debridements remain the procedure of choice. The ideal timing of free flap coverage for these wounds needs further investigation.

COMMENTS

Background

High-voltage electrical burns are found to be associated with a significant morbidity leading to severe socioeconomic implications. Considering the conflicting evidence in the literature regarding progressive tissue necrosis in this devastating injury, the authors looked into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue, which can potentially prevent further progression of this pathology.

Research frontiers

The timing of flap coverage in electrical burns is debatable because of presence of progressive tissue necrosis following electrical insult. Flaps done at first debridement can fail because of progression of tissue necrosis.

Innovations and breakthroughs

The authors found that the phenomenon of ongoing necrosis was not halted and all their early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma. Serial debridements were required to achieve viable tissue bed. In addition distant pedicled flaps also allowed for safe and early coverage of hand and forearm defect and this method of reconstruction represented alternative to free tissue transfer in the presence of recipient vessel injury.

Applications

The study results suggest that electrical burns do lead to progressive tissue necrosis and any flap coverage should be contemplated after this process has stabilized.

Terminology

Progressive tissue necrosis is seen in electrical burns because of progressive microvascular thrombosis. This requires multiple stages of debridements.

Peer-review

The study on electrical burns is relatively well-presented. It is an interesting article in this field.

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SYSTEMATIC REVIEWS

Plasma-Lyte 148: A clinical review

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Abstract

AIM

To outline the physiochemical properties and specific clinical uses of Plasma-Lyte 148 as choice of solution for fluid intervention in critical illness, surgery and perioperative medicine.

METHODS

We performed an electronic literature search from Medline and PubMed (*via* Ovid), anesthesia and pharmacology textbooks, and online sources including studies that compared Plasma-Lyte 148 to other crystalloid solutions. The following keywords were used: "surgery", "anaesthesia", "anesthesia", "anesthesiology", "anaesthesiology", "fluids", "fluid therapy", "crystalloid", "saline", "plasma-Lyte", "plasmalyte", "hartmann's", "ringers" "acetate", "gluconate", "malate", "lactate". All relevant articles were accessed in full. We summarized the data and reported the data in tables and text.

RESULTS

We retrieved 104 articles relevant to the choice of Plasma-Lyte 148 for fluid intervention in critical illness, surgery and perioperative medicine. We analyzed the data and reported the results in tables and text.

CONCLUSION

Plasma-Lyte 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition

that closely reflects human plasma. Emerging data supports the use of buffered crystalloid solutions in preference to saline in improving physicochemical outcomes. Further large randomized controlled trials assessing the comparative effectiveness of Plasma-Lyte 148 and other crystalloid solutions in measuring clinically important outcomes such as morbidity and mortality are needed.

Key words: Surgery; Anesthesia; Fluid therapy; Crystalloids; Saline; Plasma-Lyte; Hartmann's; Ringers; Acetate; Gluconate; Lactate

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Core tip: Plasma-Lyte 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition that closely reflects human plasma. It is physiologically different to the commonly available crystalloids solutions such as Hartmann's solution and sodium chloride (0.9%). Before using any crystalloid solution as fluid therapy, clinicians should have a fundamental understanding of each fluids specific physiological properties.

Weinberg L, Collins N, Van Mourik K, Tan C, Bellomo R. Plasma-Lyte 148: A clinical review. *World J Crit Care Med* 2016; 5(4): 235-250 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/235.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.235

INTRODUCTION

The use of intravenous (*IV*) fluids for maintenance therapy and resuscitation in anesthesia and critical care medicine is universal. There is marked variation in perioperative fluid selection that is generally decided by institution and clinician preference. Such practice variation is related to the paucity of prospective evidence evaluating the comparative safety and efficacy of available crystalloid solutions for both fluid resuscitation and maintenance therapy in the perioperative setting. Compared to colloids, crystalloids are often the preferred solution for replacement or maintenance fluid therapy as they are relatively cheap, commonly available, easily transportable and storable with a good shelf life, and have no allergy risk. In addition, crystalloids are easy to manufacture, require no special compatibility testing, are widely available and accessible even in developing countries, and can be freely given to patients with religious objections to blood or blood related products. Currently, sodium chloride 0.9%, commonly referred to as normal saline 0.9% (NS), Ringer's Lactate and Hartmann's solution are commonly available crystalloid solutions worldwide. However, their electrolyte composition is significantly different from that of plasma[1]. In contrast, Plasma-Lyte 148 (PL 148) has physiochemical properties similar to plasma, however PL 148 has yet to be the subject of a detailed clinical review. Therefore, we present a comprehensive review of PL 148, comparing its physiochemical properties to other commonly available crystalloids solutions and evaluating its utility as a buffered fluid solution. We also discuss the role of PL 148 solution in critical care medicine and anesthesia.

MATERIALS AND METHODS

We performed an electronic literature search from Medline and PubMed (*via* Ovid), anesthesia and pharmacology textbooks, and online sources. The following keywords were used: "surgery", "anaesthesia", "anesthesia", "anesthesiology", "anaesthesiology", "fluids", "fluid therapy", "crystalloid", "saline", "Plasma-Lyte", "plasmalyte", "hartmann's", "ringers" "acetate", "gluconate", "malate", "lactate". Only studies that compared PL 148 to other crystalloid solutions were included. Articles in the English language with human and animal studies were considered. Date restrictions were not applied. The last electronic literature update was in December 2015. In total, after appropriate screening against the inclusion criteria, we retrieved 557 references or full-text journal articles for analysis and critical review. Three authors conducted the search and data extraction. Two authors analyzed the results. Including online journal articles and textbooks, 104 articles were included this review.

RESULTS

Description of product

PL 148, also known as Plasma-Lyte A, is a sterile isotonic non-pyrogenic IV crystalloid solution used in clinical medicine to provide water, electrolytes and calories to patients. PL 148 is a trade mark of Baxter International Inc. First patented in 1982, it is available in 1000 mL and 500 mL Viaflex containers and has been commercially available for peri-operative fluid intervention for over 25 years in the United States, Australasia and the United Kingdom. The electrolyte composition of PL 148 more closely reflects the constituents of human plasma compared with both Hartmann's Solution and NS, and is hence considered a more "physiological" solution. It is commonly used as both a resuscitation and maintenance fluid in the critical care setting and for perioperative fluid intervention in elective and emergency surgery.

Each 1000 mL of PL 148 contains 5.26 g sodium chloride, 370 mg potassium chloride, 300 mg magnesium chloride, 3.68 g and 5.02 g of sodium acetate and sodium gluconate respectively; this equates to 140 mmol/L sodium, 5 mmol/L potassium, 1.5 mmol/L magnesium, 98 mmol/L chloride, and 27 mmol/L and 23 mmol/L of acetate and gluconate, respectively. The physiochemical properties of PL 148 compared to plasma and other commonly available crystalloid solutions are summarized

Table 1 Characteristics of common crystalloid solutions compared to human plasma

	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Acetate (mmol/L)	Gluconate (mmol/L)	Lactate (mmol/L)	Malate (mmol/L)	eSID (mEq/L)	Theoretical osmolarity (mOsmol/kg)	Actual or measured [1]osmolality (mOsmol/kg)	pH
Plasma	136-145	3.5-5.0	0.8-1.0	2.2-2.6	98-106	Nil	Nil	Nil	Nil	42	291	287	7.35-7.45
Sodium chloride (0.9%)	154	Nil	Nil	Nil	154	Nil	Nil	Nil	Nil	0	308	286	4.5-7
Compound sodium Lactate (lactate buffered)	129	5	Nil	2	109	Nil	Nil	29	Nil	29	28	278	5-7
Ringer's lactate (lactate buffered)	130	4	Nil	3	109	Nil	Nil	28	Nil	27	278	256	5-7
Ionosteril® (acetate buffered solution)	137	4	1.25	1.65	110	36.8	Nil	Nil	Nil	36.8	291	20	6.9-7.9
Sterofundin ISO® (acetate and malate buffered)	145	4	1	2.5	127	24	Nil	Nil	5	25.5	309	Not stated	5.1-5.9
Plasma-Lyte 148® (acetate and gluconate buffered)	140	5	1.5	Nil	98-106	27	23	Nil	Nil	50	295	271[2]	7.4[3]

[1]Freezing point depression; [2]Australian and New Zealand formulation; however approximate osmolality may vary depending on country of manufacture; [3]Australian and New Zealand formulation; however pH ranges from 6.5 to 8.0 depending on country of manufacture. Plasma-Lyte 148 manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ringer's Lactate manufactured by Baxter Healthcare, Deerfield, IL, United States; Hartmann's solution manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ionosteril manufactured by Fresenius Medical Care, Schweinfurt, Germany; Sterofundin ISO manufactured by B. Braun Melsungen AG, Melsungen, Germany.

in Table 1. Unlike Hartmann's solution, which contains calcium, PL 148 is calcium free and therefore compatible with blood and blood components. PL 148 contains no antimicrobial agents. The caloric content is approximately 66 kilojoules/L or 16 kcal/L. The numeric "148" is a derivative of the sum of each of PL 148's cationic concentrations, *i.e.*, 140 mEq (sodium) plus 5 mEq (potassium) plus 3 mEq (magnesium), which equates to a sum total of "148 mEq". The formulation "PL 148 (approximate pH 7.4)" is available in Australia and New Zealand. The formulation is approved by the Australian Therapeutics Goods Administration and registered in both Australia (AUST 231424 and 48512) and Medsafe (New Zealand). The pH of PL 148 is adjusted with sodium hydroxide and reported as approximately 7.4, however depending on country of manufacture, the pH ranges from 6.5 to 8.0. PL 148 is supplied in VIAFLEX™ plastic bag containers produced from a uniquely formulated polyvinyl chloride. VIAFLEX is a trademark of Baxter International Inc. Safety of the polyvinyl chloride has been confirmed in animal and tissue culture toxicology studies.

DISCUSSION

Contraindications and precautions

There are no published cases in the medical literature of PL 148 hypersensitivity reactions, however anaphylactic and hypersensitivity infusion reactions have been reported[2]. As the PL 148 bag is an adaptable or flexible plastic container, it should not be connected in series with other fluid containers due to the risks of air embolism. Pressure infuser bags to increase flow rates should be used very cautiously with any of the PL 148 containers, as any residual air in the container that has not been evacuated prior to administration, can result air embolism. Similarly, the use of open vented IV administration sets can also result in air embolism, and these should not be used with the PL 148 flexible container.

Compatibility with other IV medications

The physical compatibility of PL 148 with medications commonly used in the operating theatre and critical care settings has been investigated[3]. PL 148 was

tested with 87 drugs for physical compatibility immediately on mixing, 1 h and 4 h after mixing. Y-site compatibility was determined by visual examination performed with laboratory light. Turbidity was measured with high-intensity light using a portable turbidimeter. On mixing, visual appearance changes occurred with amiodarone, cyclosporine, propofol and mycophenolate. An increase in turbidity was observed with pantoprazole and phenytoin, amiodarone, cyclosporine, propofol and mycophenolate.

Drug interactions

Similar to all crystalloid solutions, PL 148 should be used cautiously in patients on corticosteroids due to additive risks of sodium and fluid retention. More specific to PL 148, due to its alkalinizing effects, the renal elimination of acidic drugs such as aspirin and barbiturates, or drugs such as lithium, may increase[2]. The renal elimination of alkaline drugs such as quinidine, or dextroamphetamine (dexamphetamine) and sympathomimetics (*e.g.*, ephedrine) may be decreased. At present there is insufficient evidence for any dose adjustment with any of the stated interacting drugs.

Drug and laboratory test interactions

As gluconate plays a role in the galactomannan antigenicity of PL 148, patients receiving PL 148 may test positive for the galactomannan antigen. Previous studies have reported that patients and healthy volunteers receiving PL 148 have demonstrated a false-positive circulating galactomannan test lasting for up to 24 h[4-7]. Galactomannan antigen is a biomarker for pulmonary aspergillosis in immunocompromised patients. Positive test results in patients receiving PL 148 should therefore be interpreted cautiously and the galactomannan antigen should be confirmed by other diagnostic methods[4]. More recently however, Spriet *et al*[8] tested 33 distinct batches of PL 148 and reported that with contemporary sophisticated manufacturing processes, PL 148 does not result in false-positive galactomannan test results.

Carcinogenesis, pregnancy and geriatric patients

There are no studies of PL 148 that have evaluated its carcinogenic and mutagenic potential. It is unknown if PL 148 has any effects on fertility. In the United States, PL 148 is classed as "Category C" in pregnancy. No "category" is stated in the Australian Product Information for PL 148. Drugs in "Category C" may cause harmful, but reversible effects to the fetus or neonate, however do not result in deformity or malformation. The Australian categorization system of medicines for use in pregnancy differs from the Food and Drug Administration categorization in the United States and does not follow a hierarchical structure. To date, there are no animal reproduction studies of PL 148 and it is not known if PL 148 causes foetal adverse effects when administered during pregnancy, or whether PL 148 affects reproduction capacity. There is no evidence to suggest that PL 148 is excreted in breast milk. There is insufficient information to determine if elderly patients respond differently from younger subjects. In general, dose selection of PL 148 in the elderly should take into consideration cardiac, renal, and hepatic function, together with pre-existing comorbidities and pharmacological therapy.

Physiological properties of PL 148

PL148 is marketed as a "physiological" and "balanced" fluid, because its composition closely reflects that of plasma. Its physiochemical properties are however different from the commonly used crystalloids: NS and Hartmann's solution. Outlined below are the key differences between PL 148 and these commonly available crystalloid solutions.

Osmolality: Normal plasma osmolality is 280-296 mOsmol/kg. PL 148 is an isotonic solution with an approximate osmolality of 271 mOsmol/kg (current formulation in Australia and New Zealand), as determined by an osmometer using the technique of freezing-point depression. In other countries, the stated osmolality is approximately 291 mOsmol/kg. Osmolarity is the measure of the solute concentration, or the number of osmoles of solute particles per unit volume of solution. The osmotic pressure of a solution determines how a solvent will diffuse across a semipermeable membrane (osmosis) that separates two solutions of different osmotic concentrations. The osmotic activity of IV fluids is best described by the calculated *in vivo* osmolality (mOsmol/kg) of that solution[9]. Tonicity on the other hand, is a measure of the effective osmotic pressure gradient of two different solutions that are separated by a semipermeable membrane. Therefore, tonicity can be described as the "relative concentration" of solutions, which in turn, determine the direction and degree of diffusion of that solution. The terminology is distinctive; osmolarity is the total concentration of diffusible and non-diffusible solutes, whereas tonicity takes into account the total concentration of only non-diffusible solutes.

PL 148 is considered a "balanced" fluid and isotonic with plasma, because it has a calculated *in vivo* osmolality within the normal physiological range of 270 to 290 mOsmol/kg[10]. Interestingly, NS is considered "hypertonic" with an *in-vitro* osmolality of 308 mOsmol/kg (154 mOsmol/kg Na^+, 154 mOsmol/kg Cl^-). However, as its electrolyte components are only partly active (osmotic coefficient of 0.926[9]), NS is "isotonic" (calculated *in-vivo* osmolality of 287 mOsmol/kg[11]). In contrast to both PL 148 and NS, Hartmann's solution is relatively "hypotonic" with an *in-vivo* osmolality of 254 mOsmol/kg. Fluids that are hypotonic relative to plasma, can result in retention of free water and consequent hyponatremia, effects frequently compounded by the release of anti-diuretic hormone, which is stimulated with critical illness,

anesthesia, and surgical stress[12]. Hypotonic fluids should be used extremely cautiously, if at all, in patients with fluid overload states, hyponatremia, critical illness, or in the setting of raised intracranial pressure. Failure to excrete this water load can cause postoperative fluid balances excess, weight gain, and resulting tissue edema and cellular dysfunction[13].

Chloride concentration: Normal plasma concentration of chloride ranges between 98 and 106 mmol/L. PL 148 contains a physiological amount of chloride (98 mmol/L), whilst Hartmann's solution is slightly hyperchloremic relative to plasma (109 mmol/L). In contrast, NS contains supra-physiological concentrations of chloride (154 mmol/L), with accumulating data and expert opinion supporting the view that large volumes of NS cause a normal anion gap hyperchloremic metabolic acidosis[14]. Even the infusion of IV NS over a few hours has been shown to cause a metabolic acidosis *via* this mechanism[15-19]. Whilst the development of acidosis may result in impaired cardiac contractility, arrhythmias, pulmonary hypertension, renal and splanchnic vasoconstriction and impaired coagulation[10], the physiological benefits of an acidemia include improved oxygen delivery *via* the Bohr effects and acidemic protection against hypoxic stress[10,20-22].

Hyperchloremia has recently been linked to adverse clinical outcomes in several animal and human studies. McCluskey *et al*[23] reviewed the datasets of 22851 surgical patients undergoing non-cardiac surgery with normal chloride concentration and kidney function. Postoperative hyperchloremia (defined as plasma chloride > 110 mmol/L) occurred in 22% of patients. Hyperchloremia was associated with adverse renal outcomes and 30-d mortality. Similarly, the adoption of a chloride-restriction protocol in a university hospital critical care unit was also associated with a decrease in AKI and renal replacement therapy[24]. Finally, in a trial examining outcomes in patients receiving major abdominal surgery who were administered PL 148 or NS for routine perioperative fluid intervention, there was an increased risk of major adverse events, particularly infection and acute kidney injury, among patients who received NS[25]. It was unclear if the higher incidence of AKI was due to hyperchloremia or other confounding factors. The suggested mechanisms of hyperchloremic induced kidney injury include inability of the proximal tubules to reabsorb chloride, increasing transport of chloride to the distal tubule, thereby decreasing glomerular filtration[26-28], hyperchloremic induced thromboxane[29], and inflammatory mediator and cytokine release[30].

In an animal model evaluating the effects of fluid resuscitation with NS *vs* PL 148 on acute kidney injury in sepsis, NS resuscitation resulted in significant hyperchloremia and acidemia[30]. Acute kidney injury severity was increased with NS compared with PL 148 resuscitation, and 24-h survival favored PL 148 resuscitation. In an animal model of hemorrhagic shock, resuscitation with PL 148 resulted in a more effective restoration of blood pressure, and improved biochemical profiles when compared to NS[31]. This study also showed that resuscitation with PL 148 improved renal oxygen consumption. Chowdhury *et al*[32] performed a clinical trial examining kidney blood flow and cortical perfusion in healthy participants who were given 2000 mL of NS or PL 148. Participants receiving NS had reduced renal blood flow and cortical perfusion. Furthermore, in another volunteer study participants received a fast infusion of 2000 mL of NS and renal excretion took more than 2 d[33]. This was further supported by a study by Stenvinkel *et al*[34] where healthy volunteers who received 2000 mL of NS over 2 h were noted to have a decrease in their eGFR by 10%. Recently, in a blinded, cluster randomised, double-crossover trial the renal effects of PL 148 and NS were investigated in patients admitted to four ICUs. In this trial, 1152 patients received PL 148 and 1110 patients received NS[35]. No substantial difference in AKI between the groups was reported. Adequately powered clinical trials are eagerly awaited to evaluate the efficacy of PL 148 and NS in high-risk patients that report clinically important outcomes such as major morbidity and mortality. Current research programs are underway with details on the trial designs already published[36]. There is still ongoing debate as to whether NS should be replaced with balanced crystalloids for both fluid maintenance and resuscitation to minimise acute kidney injury[37,38].

Other electrolytes: Similar to Hartmann's solution, PL 148 has a potassium content of 5 mmol/L; PL 148 should be used cautiously in patients receiving ACE inhibitors or angiotensin II receptor antagonists, calcineurin inhibitors, *e.g.*, tacrolimus, and the immunosuppressant cyclosporine, due to increase the risk of hyperkalemia. Similarly, PL 148 should be used cautiously in patients with hyperkalemia or who are predisposed to severe hyperkalemia, *e.g.*, rhabdomyolysis, severe burns, renal failure, and adrenocortical insufficiency. Unlike Hartmann's solution or Ringer's lactate, PL 148 contains 1.5 mmol/L magnesium and should be used cautiously in patients with hypermagnesemia or who are at risk of hypermagnesemia. Further, in patients receiving PL 148, magnesium levels should be checked before additional magnesium is administered. However, PL 148 is not indicated for the treatment of hypomagnesemia. Hartmann's solution contains calcium and should be used cautiously with blood or blood derivatives, due to the potential risks of precipitation and clot formation[39]. In contrast, PL 148 is calcium free and completely compatible with blood or blood components. The mixing of fluids containing calcium and magnesium with drug salts of phosphates, carbonates, tartrates or sulfates should also be avoided due to risks of forming insoluble calcium or magnesium salts. Mixing calcium-containing solutions, *e.g.*, Hartmann's with ceftriaxone can cause the formation of insoluble ceftriaxone calcium salts[40].

Strong ion difference: An important physicochemical

property of PL 148 compared to other crystalloid solutions is its ability to increase pH in patients with a pre-existing metabolic acidosis. Experimental evidence has shown that the optimal effective *in-vivo* strong ion difference (SID) for an IV fluid not to influence blood pH should be approximately 24 mEq/L[41,42]. Saline 0.9%, with its equal concentrations of sodium and chloride, has a SID of zero. It follows that infusion of NS will significantly reduce the SID of plasma, thus causing a metabolic acidosis. Hartmann's solution is considered to be a "balanced" solution compared to NS, with an effective *in-vivo* SID of 29 mEq/L. PL 148 has a SID of 50, which is the reason it is considered an "alkalinizing" solution. As PL 148 is an alkalinizing solution, its administration may increase plasma pH, which can decrease ionized calcium concentrations. Whilst PL 148 may correct an underlying metabolic acidosis, it should be administered cautiously, if at all, to patients with alkalosis.

Inorganic and metabolic anions in Plasma-Lyte 148

Acetate: Normal physiological levels of acetate are 0.06-0.2 mmol/L in plasma. The acetate concentration in PL 148 is 27 mmol/L. Acetate is no longer used as a hemodialysis buffer in modern dialysis treatments. Although initial studies showed that acetate based solutions were almost as effective as bicarbonate in maintaining acid base homeostasis in patients with cholera[43,44], more recently the use of acetate as a hemodialysis solution has been limited by its association with cardiovascular instability in patients receiving large volume renal replacement therapy[45,46]. Adverse effects of acetate are frequently observed with both high doses and high rates of acetate infusions, particularly in the setting of hemodialysis. Small quantities of acetate in dialysate solutions have been reported to cause supra-physiological acetate plasma concentrations (50 to 100 μmol/L)[47-49]. In addition, use of acetate solutions as a cardiopulmonary prime has also been reported to cause similar plasma concentrations in patients undergoing cardiac surgery[50], although it is unknown if such concentrations are associated with detrimental or adverse clinical outcomes.

Kirkendol *et al*[51] first reported that sodium acetate produced a dose-related decrease in cardiac contractility and blood pressure in a dog model. These initial reports conflicted with further laboratory research as the same investigators showed that a slow infusion of acetate failed to cause adverse hemodynamic effects[52]. Hypoxia and hypotension are reported adverse effects in patients with chronic kidney disease dialyzed with solutions containing acetate[45,53,54]. In a crossover study involving twelve patients undergoing hemo-diafiltration randomized to either acetate or bicarbonate (acetate free) dialysate, Selby *et al*[55] demonstrated that exposure to acetate free dialysate was associated with less deterioration in systemic hemodynamics, and less suppression of myocardial contractility. Similarly, Jacob *et al*[56] examined the effect of acetate on myocardial energy metabolism and reported that acetate levels of 5 mmol/L impacted negatively on fatty acid metabolism in cardiac tissue and impaired cardiac contractility. Whilst the authors cautioned that their observations might be applicable to other parenterally administered acetate solutions, there have been no human studies to support these findings[56]. In contrast, Nitenberg *et al*[57] evaluated the effect of acetate on cardiac function before and after a sodium acetate infusion during dialysis. Cardiac function improved with plasma acetate concentrations of 3.13 mmol/L. PL 148 was shown to have adverse effects in a model of animal model of hypovolemic shock. In a study comparing four resuscitation crystalloids, animals who received PL 148 had worse survival rates and higher plasma lactate concentrations compared with NS and lactated solutions[58]. Ringer's lactate was considered the most favourable crystalloid due to its lower chloride concentration when compared to NS, and absence of acetate and magnesium when compared to PL 148.

The use of PL 148 with acetate as its organic anion may confer several advantages over the lactate-containing crystalloids. One clinical advantage is that unlike lactate metabolism, acetate metabolism is not entirely dependent on hepatic function. Acetate metabolism is preserved in severe shock, in contrast to lactate metabolism, which can be significantly impaired[59]. Lactate may be an important prognostic indicator after liver resection[60], shock states and critical illness[61,62], with strong associations shown with hyperlactatemia and risk of complications and death. Acetate is metabolised more rapidly than lactate, generating bicarbonate within 15 min after its adminstration[63,64]. Acetate is also more alkalinizing than lactate, which may confer benefit in treating patients who are acidemic who require fluid intervention or resuscitation. Ekblad *et al*[65] showed that a continuous infusion of sodium acetate (3 mmol/kg per 24 h) corrected metabolic acidosis in premature infants. More recently, in a larger clinical trial of 78 critically ill trauma patients resuscitation with sodium acetate as an alternative to NS or Hartmann's solution in patients receiving acetate had stable hemodynamic profiles without evidence of hemodynamic instability at any point[66]. In the patients who received acetate, there was a rapid correction of both metabolic acidosis and hyperchloremia. Other reported advantages of acetate are that its metabolism does not depend on age[67], acetate protects against malnutrition without disturbing glucose homeostasis[68], and unlike lactated solutions, acetate does not affect glucose or insulin concentration[68,69]. The conversion of exogenously administered lactate to glucose *via* gluconeogenesis has been reported to cause significant hyperglycemia[70]. In diabetic patients, intraoperative glucose levels have been shown to double following administration of exogenous lactate solutions[71].

Gluconate: PL 148 contains 23 mmol/L of gluconate.

However, there is limited information about the physiological impact or clinical consequences of gluconate. Approximately 80% of gluconate is eliminated *via* renal mechanisms. Compared with HCO_3, lactate or acetate, gluconate exerts little, if any alkalinizing effect[51,72]; therefore its clinical effects *in vivo* as a metabolically degradable anion appear to be very limited. Gluconate may protect against post ischemic cardiac dysfunction and oxidative injury[73], however there is lack of data on acetate and gluconate levels after PL 148 administration in most surgical settings. In a phase II clinical trial of PL 148 *vs* a bicarbonate-based cardiopulmonary bypass prime solution, there was a significant increase in unmeasured anions levels after PL 148 administration, which was still present, albeit in smaller concentrations prior to cessation of CPB[74]. Liskaser *et al*[19] reported similar findings. The unmeasured anions were attributed to acetate and gluconate. Davies *et al*[50] observed that when PL 148 was administered as a cardiopulmonary bypass pump-prime fluid, there were supra-physiologic plasma levels of acetate and gluconate when compared to a bicarbonate pump prime solution. There were no significant differences in systemic inflammation (as measured by Interleukin-6 levels), and the authors advocated larger scale studies to more precisely assess this phenomenon. The implications of supra-physiological gluconate and acetate levels remain undetermined.

Specific indications for PL 148 for perioperative fluid intervention

General surgical setting: There is a paucity of large-scale prospective trials comparing PL 148 to other fluid buffered (*e.g.*, Hartmann's solution) and non-buffered (*e.g.*, NS) solutions. A summary of the clinical trials pertinent to PL 148 are summarized in Table 2. Whilst an accumulating body of retrospective studies suggest that chloride rich solutions such as NS may directly contribute to iatrogenic hyperchloremic metabolic acidosis and adverse renal outcomes[23,25,75], results from larger prospective studies are still eagerly awaited before conclusive evidence is available to influence practice regarding the use of balanced solutions over NS[36]. Based on the current literature, balanced solutions appear to be more physiological than NS, however at present there is insufficient evidence from clinical trials to unequivocally prove that balanced or buffered crystalloid solutions are associated with improved patient outcomes. Further, at present, there is also insufficient evidence to advocate for the routine use of PL 148 over other commercially available buffered or non-buffered crystalloid. Understanding the physicochemical properties of PL 148 is paramount, as this will allow clinicians to individualise its use taking into consideration patients' comorbidity, pathology, existing fluid deficit, and concurrent biochemical derangements.

Diabetic ketoacidosis: PL 148 may have a beneficial role in patients who present in diabetic ketoacidosis[76,77]. In a randomized controlled clinical trial, diabetic patients admitted to the emergency department with ketoacidosis were resuscitated with either PL 148 or NS. Use of PL 148 prevented the development of a hyperchloremic metabolic acidosis[76]. This study did not comment on glycemic control or overall outcomes of the patients. In a similar study by Chua *et al*[77], the outcomes of patients with diabetic ketoacidosis admitted to three major critical care centres across Australia who received PL 148 or NS were evaluated. Use of PL 148 was associated with a more rapid improvement in metabolic acidosis than those who received NS. Patients receiving PL 148 had less hyperchloremia, improved mean arterial pressure, and higher cumulative urine output. Despite a more rapid improvement in metabolic acidosis, no difference was found in overall glycemic control or length of stay in ICU based on the choice of fluid administered.

Brittle diabetic patients: Unlike lactate metabolism, the metabolism of acetate does adversely affect insulin or glucose homeostasis[68,69]. PL 148 may therefore confer clinically advantages in brittle diabetic patients. In contrast, when lactate was supplied exogenously in solutions, gluconeogenesis was the principal metabolic pathway for lactate metabolism[78,79]. Plasma lactate levels as low as three mmol/L significantly increased the rate of gluconeogenesis from exogenously supplied lactate[80]. Although healthy volunteers showed no increase in glucose concentrations following lactate infusion[78,80,81], patients undergoing major surgery receiving lactated solutions can have significant intra-operative increases in blood glucose levels[70]. In diabetic patients, intraoperative glycemic control may also be significantly impaired following the administration of lactate containing solutions[71].

Liver resection and liver transplantation: The use of lactate free solutions in patients undergoing major liver surgery may be beneficial for several reasons. First, the metabolism of acetate into bicarbonate is not entirely dependent on liver metabolism, in contrast to lactate metabolism, which is more reliant on adequate liver metabolism[59]. Lactated solutions may therefore be inadequately metabolized during the anhepatic phase of liver transplantation, during major liver resection surgery or in patients with acute or chronic liver insufficiency undergoing major surgery. Plasma lactate levels are also an important prognostic marker after liver resection[60], shock states and critical illness[61,62,82]. Two recent studies evaluating fluid intervention in patients undergoing major liver resection supported the notion that lactate in Hartmann's solution can independently increase lactatemia[83,84]. A randomised controlled trial involving 104 donors undergoing right hepatectomy compared acid base status, lactate concentrations and liver function test of patients who received PL 148, or Hartmann's solution[83]. PL 148 resulted in lower lactate and bilirubin levels, lower prothrombin times, and higher albumin levels compared to patients receiving Hart-

Table 2 Summary of the Plasma-Lyte 148 clinical trials

Ref.	Title	Objectives	Patient numbers	Findings
Liskaser *et al*[19]	Role of pump prime in the etiology and pathogenesis of CPB-associated acidosis	RCT that compared the development of metabolic acidosis in patients on CPB who had either Hemaccel- Ringer's Solution, or PL 148 as the pump prime fluid	n = 22	All patients developed a metabolic acidosis when the pump prime fluid was delivered Participants who received Hemaccel-ringer's solution developed a hyperchloremic metabolic acidosis, however participants who received PL 148 developed acidosis as a result of an increase in unmeasured ions, likely acetate and gluconate The acidosis was reversed more quickly with PL 148 compared to NS
Yunos *et al*[24]	The biochemical effects of restricting chloride-rich fluids in intensive care	This study evaluated the acid base effects of administration of chloride-restricted fluids to critically ill patients, compared with unrestricted fluid management	n = 1644	Restriction of chloride rich fluids was associated with a reduction in metabolic acidosis (P < 0.001), standard base excess (P < 0.001) and severe acidemia (P < 0.001) The intervention was associated with a greater incidence of severe metabolic alkalosis (P < 0.001)
Shaw *et al*[25]	Major complications, mortality, and resource utilization after open abdominal surgery: NS compared to PL	This observational study compared the post-operative complications, in-hospital mortality and resource utilization after abdominal surgery between patients who received either NS or PL 148 fluid therapy on the day of surgery	n = 31920	Patients who received PL 148 had lower rates of in-hospital mortality (P < 0.001) and major complications (including renal failure requiring dialysis (P < 0.001), post-operative infection (P < 0.006), blood transfusions (P < 0.001), electrolyte disturbance (P < 0.046) and acidosis investigation (P < 0.001) and intervention (P = 0.02)
Aksu *et al*[31]	Balanced *vs* unbalanced crystalloid resuscitation in a near-fatal model of hemorrhagic shock and the effects on renal oxygenation, oxidative stress, and inflammation	Animal study in which rats were induced into hemorrhagic shock, and were then resuscitated with either no fluid, PL 148 or NS	n = 6	Both PL 148 and NS restored blood pressure during resuscitation NS was associated with hyperchloremia (P < 0.001) and metabolic acidosis (P < 0.05) PL 148 restored acid base balance more effectively than NS PL 148 was associated with improvement in renal oxygen consumption occurred compared to NS (P < 0.05) Systemic inflammation and oxidative stress were similar with NS or PL 148
Chowdhury*et al*[32]	A randomized, controlled, double blind crossover study on the effects of 2L infusions of NS and PL on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers	The authors used MRI to compare the renal blood flow of healthy male volunteers following a 2L infusion of either PL 148 or NS	n = 12	NS was associated with hyperchloremia (P < 0.0001) and metabolic acidosis (P < 0.025) NS was associated with a decrease in a reduction in mean renal artery flow velocity (P = 0.045) and renal cortical tissue perfusion (P = 0.008), findings not observed after PL 148
Young *et al*[35]	Effect of a buffered crystalloid solution *vs* saline on acute kidney injury among patients in the Intensive Care Unit: The SPLIT randomized clinical trial	A double blind, cluster randomized, double-crossover trial conducted in 4 intensive care units. The primary aim was to determine the effects of PL compared with NS on renal complications	n = 2278	No differences in the incidence of acute kidney injury (P = 0.77) No differences in mortality (P = 0.40)
Omron *et al*[42]	A physicochemical model of crystalloid infusion on acid-base status	In this study, authors used a simulated human model in a standard physiological state to compare the effect of 5 different fluids with varying SID values on the acid-base status of the human model when infused up to 10 L	n = 1	Solutions with a SID greater than 24.5 mEq/L resulted in a progressive metabolic alkalosis Solutions with a SID less than 24.5 mEq/L resulted in a progressive metabolic alkalosis PL 148 (SID of 50 mEqu/L) caused a progressive metabolic alkalosis when administered in high volumes

Davies *et al*[50]	Plasma acetate, gluconate and interleukin-6 profiles during and after CPB: A comparison of PL 148 with a bicarbonate-balanced solution	In this study, acetate levels were compared in elective cardiac surgical patients who received either PL 148 or a bicarbonate- balanced crystalloid as the priming fluid for their cardiopulmonary bypass	n = 30	PL 148 was associated with supraphysiological plasma concentrations of acetate (P < 0.0005) and gluconate (P < 0.0005) after institution of CPB Gluconate levels remained persistently elevated at the end of CPB Plasma concentrations of acetate did not completely return to normal levels until 4 h post separation from CPB There were no significant differences in concentrations of IL-6 between the two priming fluids
Traverso *et al*[58]	Fluid resuscitation after an otherwise fatal hemorrhage: I. Crystalloid solutions	An animal model in of hemorrhagic shock comparing four crystalloid solutions (NS, Ringer's lactate, Plasmalyte-A, and Plasmalyte-R) to prevent death after a fatal hemorrhage	n = 116	Ringers lactate provided the best survival when compared to saline and PL After analyses of arterial blood gas values, biochemistry variables, and hemodynamic metrics such as heart rate and aortic pressure, Ringers lactate was considered the most superior crystalloid solution (P value: not stated)
Morgan *et al*[74]	Acid-base effects of a bicarbonate-balanced priming fluid during cardiopulmonary bypass: comparison with PL. A randomised single-blinded study	In this RCT, the authors compared the acid- base effects of a bicarbonate-balanced trial crystalloid with those of PL when administered as a 2-L prime in patients undergoing elective cardiac surgery	n = 20	PL 148 was associated with a metabolic acidosis (P = 0.0001) and an increased strong ion gap secondary to a surge of unmeasured anions (likely acetate and gluconate)
Yunos *et al*[75]	Association between a chloride-liberal *vs* chloride-restrictive IV fluid administration strategy and kidney injury in critically ill adults	This study assessed the rates of kidney injury in patients admitted to ICU who received only chloride- restricted fluids such as PL 148 or Hartmann's solution compared to those that also received fluids that were high in chloride concentration, including NS	n = 1533	The incidence of acute kidney injury decreased significantly in patients who received a chloride-restrictive fluid plan compared to those who received fluids high in chloride concentration (P < 0.001) No differences in hospital mortality, hospital or ICU length of stay were observed
Mahler *et al*[76]	Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis	In this prospective single centre study, patients admitted to the emergency department in diabetic ketoacidosis were resuscitated over at least 4 h with either NS or PL 148, and their serum chloride and bicarbonate levels were monitored and compared	n = 45	Resuscitation with NS was associated with higher serum chloride concentrations (P < 0.001) and lower bicarbonate concentrations (P = 0.020) Resuscitation with PL 148 prevented hyperchloremic metabolic acidosis
Chua *et al*[77]	PL 148 *vs* NS for fluid resuscitation in diabetic ketoacidosis	In this retrospective study, the authors compared the plasma biochemistry, hemodynamic and glycemic control in patients admitted to the ICU for management of ketoacidosis who were resuscitated primarily with PL 148 or NS over the first 12 h	n = 23	PL 148 was associated with less hyperchloremia and a more rapid improvement in metabolic acidosis than those who received NS (P < 0.05) PL 148 improved hemodynamic measures including an improved mean arterial pressure at 2-4 h, and higher cumulative urine output at 4-6 h compared the NS group (P < 0.05) No differences were observed in glycemic control or length of stay in ICU based
Shin *et al*[83]	Lactate and liver function tests after living donor right hepatectomy; a comparison of solutions with and without lactate	A randomised controlled compared the acid- base status, lactate levels and liver function tests in patients undergoing hepatectomy for liver transplant who received PL 148 or Hartmann's solution	n = 104	Immediately post hepatectomy, donors who received PL 148 had significantly lower lactate levels (P = 0.005), lower bilirubin concentrations (P < 0.001), shorter prothrombin time (P = 0.009), and higher albumin levels compared to the Hartmann's group There were no significant differences between the groups in albumin, bilirubin, or prothrombin times on post-operative day 5 There were no significant differences in complications or duration of hospital stay

Weinberg *et al*[84]	The effects of PL 148 *vs* Hartmann's solution during major liver resection: a multicentre, double blind, randomized controlled trial	Multicentre RCT investigating the biochemical effects of Hartmann's solution or PL 148 in patients undergoing major liver resection. Primary outcome: Base Excess immediately after surgery. Secondary outcomes: changes in blood biochemistry and hematology	n = 60	Base excess similar in both groups at completion of surgery (P = 0.17) Postoperatively patients receiving Hartmann's solution were more hyperchloremic (P = 0.01) and hyperlactatemic (P = 0.02) Patients receiving PL 148 had higher plasma magnesium levels (P < 0.001) and lower ionized calcium levels (P < 0.001) No significant differences in pH, bicarbonate, albumin and phosphate levels PT and aPTT were significantly lower in the PL 148 group (P < 0.001, P = 0.007)
MacFarlane *et al*[85]	A comparison of PL 148 and NS for intra-operative fluid replacement	RCT that compared the pre-op and post-operative acid base status of patients who received either NS or PL 148 whilst undergoing major hepatobiliary or pancreatic surgery	n = 30	Intra-operatively, NS was associated with increased plasma concentrations of chloride (P < 0.01), decreased levels of bicarbonate (P < 0.01), and an increased base deficit (P < 0.01), compared to PL 148 Less blood loss and higher postoperative hemoglobin in the PL 148 group) (P = 0.03) Total complications were more frequent in the Hartmann's group (P = 0.007) Hyperchloremic metabolic acidosis occurred in patients receiving NS but not in those receiving PL 148
Hadimioglu *et al*[87]	The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation	A blinded RCT investigating the effects of NS, lactated Ringer's, or PL 148 on changes in acid-base balance, potassium and lactate levels during kidney transplantation. Urine volume, serum creatinine, and creatinine clearance were recorded on postoperative days 1, 2, 3 and 7	n = 60	Patients receiving NS had lower pH levels, and higher chloride levels (P value not stated) Lactate levels increased significantly in patients who received Ringer's lactate (P value not stated) No significant changes in acid-base measures or lactate levels occurred in patients who received PL 148 Potassium levels were not significantly changed in any group The best metabolic profile was maintained in patients who receive PL 148
Kim *et al*[88]	Comparison of the effects of NS versus PL on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods	RCT compared the effects of NS and PL 148 on acid-base balance and electrolytes during living donor kidney transplantation using the Stewart and base excess methods	n = 60	Significantly lower values of pH, base excess, and effective strong ion differences during the post-reperfusion period in the NS group (P < 0.05) Hyperchloremic metabolic acidosis present in the NS group (P < 0.05) No differences between the groups in early postoperative graft function (P = 0.3)
Potura *et al*[89]	An acetate-buffered balanced crystalloid *vs* NS in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial	RCT that evaluated the impact of NS *vs* a chloride-reduced, acetate-buffered crystalloid on the incidence of hyperkalemia during cadaveric renal transplantation. The incidence of metabolic acidosis and kidney function were secondary aims	n = 150	The incidence of hyperkalemia differed by less than 17% between groups (P = 0.56) Use of balanced crystalloid resulted in less hyperchloremia (P < 0.001) and metabolic acidosis (P < 0.001) Significantly more patients in the NS group required administration of catecholamines for circulatory support (P = 0.03)
Smith *et al*[99]	Cost-minimization analysis of two fluid products for resuscitation of critically injured trauma patients	A retrospective cost-minimization analysis evaluating fluid and drug acquisition costs, materials and nurse labor costs, and costs associated with electrolyte replacement in patients who received PL 148 or NS	n = 46	Substitution of PL 148 for NS for fluid resuscitation during the first 24 hours after trauma was associated with decreased magnesium replacement requirements (P < 0.001) and a net cost benefit to the institution

Smith *et al*[100]	Does saline resuscitation affect mechanisms of coagulopathy in critically ill trauma patients? An exploratory analysis	An exploratory analysis of a subset of subjects enrolled in a randomized trial comparing the effect of resuscitation with PL 148 and NS on acidosis and electrolyte abnormalities	n = 18	Patients receiving NS were more acidemic at 6 h (mean pH saline 7.31 *vs* PL 148; base excess NS -5.3 mmol/L *vs* 0.6 mmol) (P value: not stated) Kinetics time was shorter (P = 0.06) and alpha angle was significantly greater (P = 0.008) in the PL 148 group NS did not alter endogenous thrombin potential: (P > 0.1) for all variables
Song *et al*[101]	The effect of 0.9% saline *vs* PL 148 on coagulation in patients undergoing lumbar spinal surgery; a randomized controlled trial	This study compared the effect of PL 148 to NS on coagulation assessed by rotation thrombo-elastometry (ROTEM) and acid-base balance in the aforementioned patients	n = 50	Patients receiving NS developed a transient hyperchloremic acidosis (P < 0.05) Coagulation assessed by ROTEM analysis and the amount of blood loss was similar between the groups: (P > 0.1 for all variables)
Young *et al*[102]	Saline *vs* PL in initial resuscitation of trauma patients: a randomized trial	RCT that evaluated the acid-base status of patients who were resuscitated with either PL or NS for the first 24-h post major trauma	n = 46	Significantly greater improvement in base excess (estimated difference 4.1 mmol/L) and less hyperchloremia (estimated difference 7 mmol/L) in patients who were resuscitated with PL compared to those resuscitated with NS (P value: not stated)
Story *et al*[103]	Cognitive changes after saline or PL 148 infusion in healthy volunteers: a multiple blinded, randomized, crossover trial	Randomized, crossover, blinded study of healthy adult volunteers. On separate days, participants received 30 mL/kg over 1 h of either NS or PL. Primary endpoint: reaction time index after infusion - a validated metric of cognitive function	n = 25	NS was also associated with greater metabolic acidosis (P < 0.001) NS was also associated with higher serum chloride levels (P < 0.001) No difference in measures of cognition after infusions of PL 148 or NS (P = 0.39)
Noritomi *et al*[104]	Impact of PL 148 pH 7.4 on acid-base status and hemodynamics in a model of controlled hemorrhagic shock	After controlled hemorrhagic shock was induced, animals were resuscitated with NS, Ringer's lactate solution or PL 148	n = 18	Resuscitation with all three fluids restored cardiac output, and urinary output Resuscitation with PL 148 and Hartmann's Solution both resulted in a reduction in chloride concentration, and increased base excess Resuscitation with NS was associated with an increased chloride concentration (P = 0.018), reduction of base excess (P = 0.042) and a metabolic acidosis (P = 0.045)

PL 148: Plasma-Lyte 148; NS: Normal saline 0.9%; RCT: Randomized clinical trial; CPB: Cardiopulmonary bypass; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; SID: Strong ion difference; ICU: Intensive care unit; IL: Interleukin.

mann's solution. In this single centre study no significant differences in complications or duration of hospital stay between groups were reported. Recently, however, in a multicentre trial evaluating patients undergoing major liver resection[84], patients who received PL 148 had improved biochemical and hematological profiles (acid base homeostasis, electrolyte balance and coagulation status) as well as fewer complications and reduced length of stay. Finally a smaller study by McFarlane *et al*[85] compared the pre-op and post-op acid base status of patients who received either NS or PL 148 whilst undergoing major hepatobiliary or pancreatic surgery. Consistent with the other studies above, patients who received NS intra-operatively were more hyperchloremic and acidemic compared to those who received PL 148. The most favourable crystalloid solution for patients undergoing major liver surgery is still unknown[86].

Renal transplantation: Traditionally, NS is advocated peri-operatively for renal transplant recipients due to concerns about hyperkalemia from balanced solutions, which contain potassium. Although NS is widely advocated in this setting, recent evidence suggests balanced crystalloids such as PL 148 or Hartmann's may be more appropriate. Hadimioglu *et al*[87] performed a randomised clinical trial comparing PL 148, Hartmann's solution, and NS as intraoperative fluid replacement in 90 patients undergoing renal transplant. Those receiving NS had higher chloride, lower pH and lower base excess than the other two groups. Those patients receiving Hartmann's had elevated lactate levels. Potassium levels, urine output, serum urea and creatinine and creatinine clearance were similar between the groups. The authors concluded that all three fluids appear safe in short-duration uncomplicated renal transplant surgery, but the metabolic profile was best maintained with PL 148. Four other randomised controlled trials reported acid-base metrics as primary outcomes[88-91]. All were

underpowered to adequately report endpoints such as hyperkalemia, requirements for dialysis, delayed and long-term graft function, and survival. Two of these studies used an acetate based crystalloid solution for fluid intervention[89,91]. Kim *et al*[88] studied the effects of NS and PL 148 on acid-base homeostasis in patients undergoing living donor kidney transplantation. There was significant hyperchloremic metabolic acidosis in the NS group, but no difference in early postoperative graft function. More recently, Potura *et al*[89] evaluated the effects of NS *vs* a chloride-reduced, acetate-buffered solution (similar in composition to PL 148) on the incidence of hyperkalemia in 150 patients undergoing cadaveric renal transplantation. The incidence of hyperkalemia was not statistically different between the groups. However, use of the buffered solution resulted in less hyperchloremia and metabolic acidosis, and a lower requirement for vasoactive medications.

Raised intracranial pressure and hypo-osmolar states: Administration of hypo-osmolar solutions such as Hartmann's solution may worsen cerebral oedema and increase intracranial pressure in neurosurgical patients with critical brain injury or existing raised intracranial pressure. Larger volumes of Ringers lactate are well known to reduce plasma osmolality[92] and result in transient increases in intracranial pressure[93]. The magnitude of the increase in intracranial pressure can be predicted from the reduction of plasma osmolality[9]. In animal models, for every mOsmol/kg reduction in plasma osmolality, there is a mean increase in intracranial pressure of 1.5 mmHg[92,94-98]. Iso-osmolar solutions such as PL 148 or NS may not impact on plasma osmolality to the same extent as hypo-osmolar solutions and may be advantageous in this setting. PL 148 may be advantageous compared to Hartmann's solution in the setting of fluid overload states and iso-osmolar hyponatremia, such as that which occurs in transurethral resection of the prostate syndrome. Given NS's greater tonicity compared to PL 148, NS may be the preferred crystalloid in this setting.

Costs of Plasma-Lyte 148

Currently the net acquisition cost of PL 148 varies significantly between different countries and even between different states within the same country. In Australia, list prices and actual hospital acquisition price differ in accordance with state, individual hospital, local tenders and preferred supplier agreements. In New Zealand, there is different pricing again due to the Pharmaceutical Management Agency, which actively manages government spending on medicines in order to maximize value for medicines, achieving the best health outcomes for the amount of public money spent. In Australia and New Zealand net acquisition costs of 1000 mL PL 148 varies between $2.00 and $5.00; in other countries such as China and South Korea prices appear to be similar. In contrast, net acquisition costs for a 1000 mL bag of Hartmann's solution or NS is Australia is currently less than $2.00. Recently, a retrospective cost-minimization analysis evaluated drug acquisition and expenses related with electrolyte replacement in critically injured trauma patients treated with NS or PL 148[99]. The use of PL 148 was associated with a higher fluid acquisition costs and a decreased need for magnesium supplementation[100]. Considering consumable supplies and nursing labor costs, there was a $12.35 daily cost-differential in patients who received PL 148. Substitution of PL 148 for NS was correlated with reduced magnesium supplementation therapy and overall net cost-benefits for the hospital.

In conclusion, administration of IV fluids is fundamental to the optimal management of patients in anesthesia and critical care medicine. The selection of the appropriate fluid for administration is often based on clinician preference, and to date there is a lack of large-scale prospective research comparing the safety, efficacy and indications of the different types of crystalloid solutions. Whilst NS is the most common IV fluid crystalloid worldwide, large-scale observational studies and small-randomized trials suggest a strong association between its use and adverse biochemical and clinical outcomes. Emerging data supports the use of buffered crystalloid solutions in preference to NS in improving physicochemical outcomes; however currently there is insufficient evidence to recommend this change in practice. Further large randomized controlled trials assessing the comparative effectiveness of PL 148 and NS in higher risk patients by measuring clinically important outcomes such as mortality are currently underway[36].

Use of PL 148 should be based on a detailed knowledge of its physicochemical properties, and the pathophysiological condition of the patient. The ideal approach for perioperative fluid therapy should therefore always be individualized: Qualitatively: Fluid with suitable physicochemical composition individualized to patients' physiological state and specific type of surgery, and quantitatively: The right amount of fluid at the right time and at the right rate.

COMMENTS

Background

The use of intravenous fluids for maintenance therapy and resuscitation in anesthesia and critical care medicine is universal. There is marked variation in perioperative fluid selection, frequently determined by institution and clinician preference. Such practice variation is related to the paucity of prospective evidence evaluating the comparative safety and efficacy of available crystalloid solutions for both fluid resuscitation and maintenance therapy in the perioperative setting. The authors present a comprehensive review of Plasma-Lyte 148 (PL 148), comparing its physiochemical properties to other commonly available crystalloids solutions.

Research frontiers

PL 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition that closely reflects human plasma. Emerging data supports the use of buffered crystalloid solutions in preference to sodium

chloride (0.9%) in improving physicochemical and clinical outcomes.

Innovations and breakthroughs

There is a paucity of large-scale prospective trials comparing Plasma-Lyte 148 (PL 148) to other fluid buffered (*e.g.*, Hartmann's solution) and non-buffered (*e.g.*, sodium chloride, 0.9%) solutions. Based on the current literature, balanced or buffered solutions appear to be more physiological than sodium chloride (0.9%), however at present there is insufficient evidence from prospective clinical trials to unequivocally prove that such solutions are associated with improved patient outcomes. Further, at present, there is insufficient evidence to advocate for the routine use of PL 148 over other commercially available buffered or non-buffered crystalloid.

Applications

Unlike lactate, acetate metabolism is not entirely dependent on preserved liver function for its metabolism, and the metabolism of acetate does adversely affect insulin or glucose homeostasis. Therefore, PL 148 may more beneficial than a lactate buffered solution in critically ill patients with liver hypoperfusion, liver insufficiency, or for patients undergoing complex liver surgery. PL 148 may also be a favourable solution in brittle diabetic patients. PL 148 is a more alkalinising solution than sodium chloride and Hartmann's solution, and may have a role in correcting severe metabolic academic states where fluid intervention is indicated. Administration of hypo-osmolar solutions such as Hartmann's solution may worsen cerebral oedema and increase intracranial pressure in neurosurgical patients with critical brain injury or existing raised intracranial pressure. Similar to sodium chloride (0.9%), Plasma-Lyte is isotonic, and may be a suitable solution for fluid therapy in this setting. Use of PL 148 should be based on a detailed knowledge of its physicochemical properties, and the pathophysiological condition of the patient. The ideal approach for perioperative fluid therapy should be individualized: qualitatively: Fluid with suitable physicochemical composition individualized to patients' physiological state and specific type of surgery, and quantitatively: The right amount of fluid at the right time and at the right rate.

Terminology

A crystalloid solution is any solution containing electrolytes and non electrolytes. A balanced or buffered crystalloid solution is a crystalloid solution with a physiochemical composition that closely reflects human plasma.

Peer-review

The authors reviewed clinical studies of PL 148. The manuscript is valuable and well written.

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