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Original Article

The role of invasive monitoring in the resuscitation of major burns: a systematic review and meta-analysis

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Abstract: Increasingly, in major hospitals invasive monitoring endpoints are utilised to guide the acute resuscitation of burns. The aim of this review is to evaluate effects of invasive monitoring for major burns patients (>20% total body surface area) to prevent early organ dysfunction. Five databases were searched for randomised controlled trials and cohort studies that evaluated invasive monitoring within the acute phase (first 24 hours). Invasive monitoring included transesophageal echocardiogram, central venous pressure measurement, and pulmonary artery catheterisation. Primary outcomes included multiple organ failure scores, renal and cardiac dysfunction measurements, compartment syndrome and lactate at 24 hours. Secondary outcomes included mortality and intensive care unit stay. Ten studies involving 401 major burns patients were included. Data pooled from four studies demonstrated significantly improved cardiac index at 24 hours compared to non-invasive endpoints (MD: 0.65, 95% CI: 0.46-0.82, *P*=0.00001). Five studies pooled showed significantly increased urine output with invasive monitoring (MD: 0.18, 95% CI: 0.03-0.34, *P*=0.02), whereas there was no difference in blood lactate levels (MD: -0.11, 95% CI: -0.44-0.22, *P*=0.43). There was a trend for lower mortality in invasive monitoring groups compared with non-invasive controls; however, the difference was not significant. There remains insufficient evidence to determine whether invasive monitoring to guide fluid resuscitation improves patient outcomes after major burn trauma. Although meta-analysis determined significantly improved cardiac index and urine output, further studies are required.

Keywords: Burns, invasive monitoring, fluid resuscitation, trauma, organ dysfunction, shock

Introduction

Globally 11 million people suffer from burns each year, and over 300,000 will die [1, 2]. Death primarily occurs from burns shock within 72 hours [3] as a result of a decrease in blood volume from fluid loss, systemic inflammation, coagulopathy and organ dysfunction, particularly cardiovascular and renal dysfunction [4, 5]. Non-fatal burn injuries are also a leading cause of morbidity [6, 7]. Fluid resuscitation is the mainstay of treatment for burns in the acute phase after injury. The goal of fluid resuscitation is to preserve organ function while avoiding complications such as compartment syndrome and pulmonary oedema from excessive fluid administration [8]. Optimising the balance of fluid requirements in major burns patients is the goal of current research into the volume, type and endpoint of fluid resuscitation. The modified Parkland formula with a targeted urine output of >0.5 ml/kg/hr has traditionally been considered the standard of care in the acute resuscitation of burns [9-11]. However, hourly urine output in burns resuscitation has been found to have no survival advantage over the use of hemodynamic monitoring [12]. With the advancement of invasive hemodynamic monitoring in critical care such as transpulmonary thermodilution (TPTD) and transoesophageal echocardiogram, it has potential application for resuscitation in the acute phase of burns [13-15]. In the intensive care setting TPTD and echocardiogram allow for multiple endpoints of cardiac function to be quantified [16]. TPTD commonly uses a Pulse Index Continuous Cardiac Output (PICCO) system (Pulsion Medical Systems SE, Munich, Germany) or the Lithium Dilution Cardiac Output (LiDCO™) system (LiDCO Ltd., Cambridge, UK),

that measures mean arterial pressure (MAP), Cardiac output (CO)/Cardiac index (CI), Systemic Vascular Resistance Index (SVRI), end-diastolic volume (EDV), and extravascular lung water index (EVLWI) [14, 16]. The use of echocardiogram in fluid resuscitation allows for monitoring of changes in ventricular EDV and central venous pressure (CVP), and measurement of the inferior vena cava (IVC) diameter to assess volume status [17]. Although invasive monitoring provides a range of vital parameters for goal-directed resuscitation, it has not been validated in burns patients, and to date, no systematic reviews have been completed on the subject. To address this gap, we conducted a systematic review and meta-analysis to identify the effect of early invasive monitoring of patients with major burns (>20% total body surface area) on goal-directed resuscitation to preserve organ function. This review provides summary results of the use of invasive monitoring in the acute setting of burns (first 24 hours) and its effect on organ dysfunction and mortality.

Materials and methods

Systematic review

This systematic review was conducted and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [18]. A review protocol was registered and published with PROSPERO (registration number: CRD42018105269), an international prospective register for systematic reviews.

Eligibility criteria

All studies of major burns fluid resuscitation that used invasive monitoring during the acute resuscitation of major burns were included. Primary outcome measures of organ dysfunction in the first 24 hours were organ dysfunction score, renal or cardiac dysfunction, blood lactate levels, and abdominal compartment syndrome. The detailed search strategy is outlined in **Appendix 1**. Secondary outcome measures included mortality and length of stay (LOS) in the intensive care unit (ICU). This review defined acute intervention as the first 24 hours post-burn; if a time point was not specified all attempts to contact the author(s) were made to determine timing. Only studies that reported fluid resuscitation of burns covering a surface area greater than 20% in adult patients were included. There were no restrictions placed on study size, language, or date of publication. Animal studies, case studies, review articles and conference abstracts were excluded from this review.

Information sources

The literature search was conducted on publications available up to January 4, 2019. Five databases were searched: Scopus (1996-present), MEDLINE (1946-present), EMBASE (1947-present), ClinicalTrials.gov, and Cochrane. Reference lists of studies that were retrieved in full text were also hand searched to identify any additional studies. Where possible, the authors of the included studies were contacted to find additional papers and unpublished data.

Study selection

After duplicate studies were removed, two investigators screened the titles and abstracts of all retrieved citations to identify studies that potentially met the inclusion criteria. Studies judged relevant were retrieved in full text and were further reviewed by the same two investigators for inclusion and relevance. The full text of any studies for which a definite decision could not be made from the title and abstract alone was also retrieved. If any disagreement about the eligibility of certain studies could not be decided a third investigator was consulted to determine its eligibility.

Data extraction and analysis

Two investigators extracted the necessary information from identified papers using a standard form developed specifically for this review. Data were extracted for: General characteristics (authors, year, title, journal, type of publication), Study characteristics (study design, sample size), Patient characteristics (age, gender, ethnicity, location, weight), Injury characteristics (blast injury, scald, flame, thermal burn, fire, inhalation), Clinical characteristics (total body surface area [TBSA as a %], burn depth, delay time until resuscitation), Intervention type (invasive technique for monitoring, protocol used to determine resuscitation, fluid type, fluid volume), Outcome data that was reported at 24 hours (organ dysfunction, renal function,

cardiac function, abdominal compartment syndrome, blood lactate levels), as well as mortality and length of ICU stay. Summary statistics were extracted when available. There was a propensity for studies that included a wide range of major burn from 15-80% TBSA together, and no differential of the timing of fluid administered (4-48 hours); wherever possible, only the data for resuscitation in the first 24 hours with a major burn (>20%) are shown; however, this was not possible in all cases. Data are presented as mean ± standard deviation unless otherwise indicated, and rbiostatistics.com was used for conversion of descriptive statistics.

Quality assessment

An adapted Newcastle-Ottawa tool for quantitative research was adopted for the quality assessment (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Our tool included assessments of the following study characteristics: patient population source and suitability, surface area calculation (formula/charts), research methodology, reported sample size calculation, data collection, range of %TBSA included/excluded in the study, whether validated tools were used to measure organ dysfunction, and whether time to initiate treatment of burns injury was measured and reported in a reliable manner. Each study was assessed as low, moderate, or high quality.

Assessment of risk of bias

Two independent reviewers assessed the risk of bias of each included study using the Cochrane collaboration tool (http://handbook-5-1.cochrane.org). Evaluation of possible bias included generation and concealment of the allocation sequence, blinding, incomplete outcome data, selective outcome reporting and other sources of bias, with each criterion assessed as high risk, low risk, or unclear risk. In cases of disagreement the two review authors discussed the assessment until a shared decision was reached. Publication bias was planned using funnel plots if there was sufficient studies (N≥10) to explore systematic heterogeneity.

Meta-analysis method

The meta-analysis was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology Group guidelines [19]. All computations were performed using the Review Manager version 5.3 statistical software (https://community.cochrane.org/help/tools-and-software/revman-5). Due to multiple endpoints across a small number of studies a combined analysis of randomised controlled trials (RCT) and observational studies was conducted. The outcome measures analysed were: (1) urine output (UO) at 24 hours as a measure of kidney function; (2) cardiac index (CI) at 24 hours as a measure of cardiac function; (3) blood lactate at 24 hours as a measure of tissue hypoxia; and (4) mortality. Due to anticipated small sample size and differences in the invasive monitoring technique across studies, a random effects meta-analysis was undertaken to account for inherited variability. The mean difference of continuous primary outcomes of organ dysfunction (UO, CI, and lactate) and the relative risk for the secondary outcome (mortality) with associated 95% confidence intervals are reported. Statistical heterogeneity was determined by a statistically significant Chi^2 ($P<0.05$), and using the I^2 statistic ($I^2<25\%$, low heterogeneity; $I^2=25\text{-}50\%$, moderate heterogeneity; $I^2>50\%$, substantial heterogeneity) (http://handbook-5-1.cochrane.org). Statistical significance was defined at the conventional 5% level.

Results

The initial databases search produced 1,712 articles, leaving 1,382 unique articles when duplicates were removed (**Figure 1**). In total, 51 articles were examined in full text, after titles and abstracts were screened. No additional articles were obtained through contact with the authors and no new articles were obtained through reference list searching. Based on our eligibility criteria, we included 10 studies involving 401 major burns patients (**Table 1**). All 10 studies investigated the use of the invasive TPTD monitoring for goal-directed resuscitation. No studies were identified that used echocardiogram to guide fluid resuscitation. All 10 studies were relatively small with number of participants ranging between N=24 and N=132, and two studies [20, 21] were observational cohort studies without a control group (**Table 1**). Eight studies remained for meta-analysis, however not all studies reported all outcome measures.

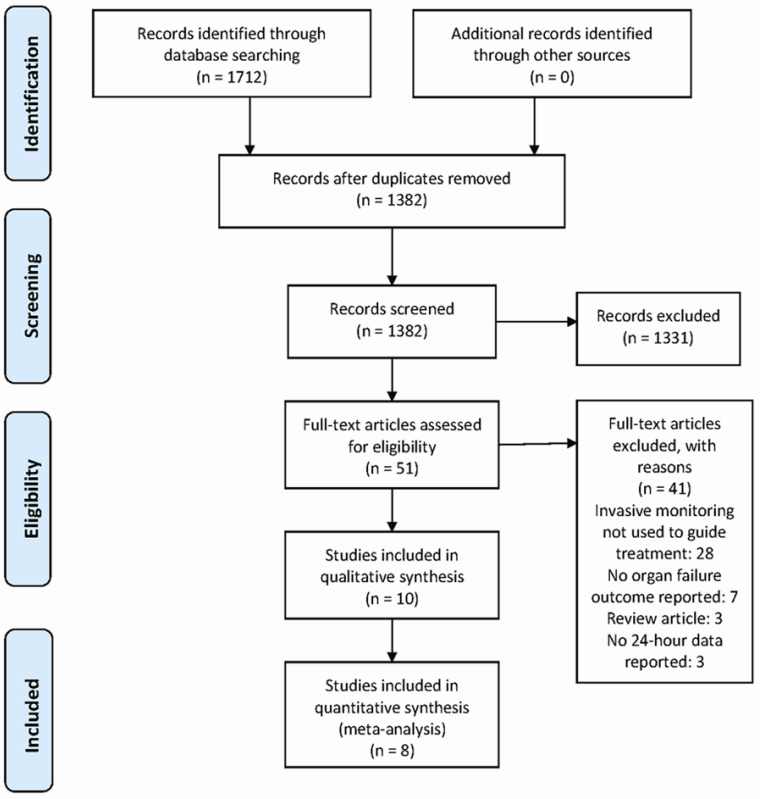

Figure 1. PRISMA flow-chart. A total of 1382 studies were evaluated for effects of invasive monitoring endpoints in fluid resuscitation of major burns patients. Titles and abstracts were assessed, and 51 full-text articles were eligible for evaluation. 41 articles were excluded, and 10 articles remained for the systematic review.

Quality and bias assessment

Quality assessment showed nine medium quality and one low quality study (**Table 2**). From 10 included studies, there were five RCTs [22-26], three prospective cohort studies [21, 27, 28], one retrospective cohort study [20], and one retrospective case series [29] (**Table 1**). Four studies determined sample size using *a priori* power analysis [23-26]. Only two studies, Foldi (2009) [24] and Csontos (2008) [25], stated a method for calculating the total body surface area burned using the Lund-Browder chart. Two studies included patients with severe burns [21, 29], with Chen primarily studying severe burns (>80% TBSA) [29]. All other studies excluded burns patients that were predicted not to survive the acute phase, with one study excluding patients if death occurred in the first seven days [24]. By combining RCTs and cohort studies in the review there is an increased risk of bias, however individual studies had a low level of bias.

General information of study population

The average age of the study population ranged from 30.4 to 52.9 years old, with a maximum age of 96 years in the study of Holm (2004) [26] (**Table 3**). Seven studies reported sex distribution with males predominant in all studies (65-92%). All studies had a mean TBSA>31.1%, with no reported differences in the TBSA between control and invasive monitoring groups in any study (**Table 3**). All 10 studies administered crystalloid fluid for resuscitation, with four studies also using colloids within the first 24 hours post-burn (**Table 3**). Three studies which used the intrathoracic blood volume index (ITBVI) to guide resuscitation had significantly higher rates of fluid administration (ml/kg/TBSA%) in the first 24 hours [23-25], whereas Chen (2017) [29] and Arlati (2006) [28] reported significantly lower fluid rates in their invasive monitoring groups compared to the control group (**Table 3**).

Multiple organ failure

No study included in this review reported significant differences in the organ dysfunction score in the first 24 hours. Since there was no standard definition of multiple organ failure used across the studies, no valid comparisons could be made and no original data were tabulated in this review. Soussi (2016) [20] reported a lower sequential organ failure assessment (SOFA) score on day one (mean 3; range 1-4), compared to Sánchez (2013) [21] (4.38±3.09), while Tokarik (2013) [22] found no significant difference between invasive monitoring and control groups at 24 hours (Invasive: 5±1 vs. Control: 5±2; *P*=0.9*).* Foldi (2010) [23] and Csontos (2008) [25] reported a multiple organ dysfunction score (MODS) at 24 hours and reported no statistical differences (Foldi, 2010: Invasive: 3.5 (3.0-5.0); Control: 4.0 (2.0-5.0)

Table 1. Summary of study characteristics

Author, year	Study design	Patients (Control:Invasive)	Control definition	Invasive endpoint definition
Chen, 2017 [29]	Retrospective case series	34 (21:13)	PLA General Hospital formula*	PICCO: CVP: 8-12 cm H_2O; MAP: >65 mmHg; UO: >1 ml/kg/hr; EVLWI: 3-7 ml/kg
Soussi, 2016 [20]	Retrospective cohort	40	No control	PICCO: MAP: >65 mmHg; UO: 0.5-1 ml/kg/hr; CI: 2.5-3 L/min/m^2; ScvO2: >70%
Aboelatta, 2013 [27]	Prospective cohort	30 (15:15)	Modified Parkland: 3 ml × TBSA% × kg	PICCO: ITBVI: >800 ml/m^2; CI: >3.5 L/min/m^2
Sánchez, 2013 [21]	Prospective cohort	132	No control	PICCO: ITBVI: 600-1000 ml/m^2; CI: >2.5 L/min/m^2
Tokarik, 2013 [22]	RCT	21 (11:10)	Brooke/Parkland: 3/4 ml × TBSA% × kg; UO: >0.5 ml/kg/hr	LiDCO: MAP: >65 mmHg; UO: >0.5 ml/kg/hr; Variation systolic BP: >10 mmHg; Variation pulse pressure: >15%; Variation stroke volume: >15%
Foldi, 2010 [23]	RCT	30 (15:15)	UO: >0.5-1 ml/kg/hr	PICCO: ITBVI: 800-850 ml/m^2
Foldi, 2009 [24]	RCT	16 (8:8)	UO: >0.5-1 ml/kg/hr	PICCO: ITBVI: 800-850 ml/m^2
Csontos, 2008 [25]	RCT	24 (12:12)	UO: >0.5 ml/kg/hr	PULSIOCATH: ITBVI: 800-850 ml/m^2
Arlati, 2006 [28]	Prospective cohort	24 (12:12)	Parkland: 4 ml × TBSA% × kg	PICCO: CI: 2.2 L/min/m^2; CVP: <4 mmHg; UO: 0.5-1 ml/kg/hr; MAP: >70 mmHg
Holm, 2004 [26]	RCT	50 (25:25)	UO: >0.5 ml/kg/hr; MAP: >70 mmHg; CVP: 2 cm H_2O	COLD: ITBVI: >800 ml/m^2; CI: >3.5 L/min/m^2

RCT = randomised controlled trial; TBSA = total burn surface area; UO = urine output; MAP = mean arterial pressure; BP = Blood pressure; CVP = central venous pressure; PICCO = Pulse Index Continuous Cardiac Output; LiDCO: Lithium Dilution Cardiac Output; EVLWI: extravascular lung water index; CI = cardiac index; ScvO2 = central venous oxygen saturation; ITBVI = intrathoracic blood volume index. *not defined.

Table 2. Quality and risk assessment

Author, year	Time frame for inclusion	States method of calculating SA	Excludes severe burns	>100 patients	Modified Ottawa Score (Oxford level of evidence)
Chen, 2017 [29]	<6 h	No	No	No	16/23 (4)
Soussi, 2016 [20]	<8 h	No	Yes	No	19/23 (2b)
Aboelatta, 2013 [27]	<6 h	No	Yes	No	18/23 (2b)
Sánchez, 2013 [21]	<8 h	No	No	Yes	16/23 (2b)
Tokarik, 2013 [22]	<24 h	No	Yes	No	15/23 (2b)
Foldi, 2010 [23]	<3 h	No	Yes	No	17/23 (2b)
Foldi, 2009 [24]	<3 h	Yes	Yes	No	18/23 (2b)
Csontos, 2008 [25]	<3 h	Yes	Yes	No	19/23 (2b)
Arlati, 2006 [28]	<6 h	No	Yes	No	18/23 (2b)
Holm, 2004 [26]	<6 h	No	Yes	No	19/23 (2b)

Time frame for inclusion defined as time between burn injury and initiation of fluid resuscitation. SA = surface area. Modified Ottawa score (≤15 low, 16-19 moderate, ≥20 high). Oxford level of evidence (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

and Csontos, 2008: Invasive: 3.5 (3.0-5.0); Control: 4.0 (2.0-5.0)).

Renal function

No studies reported renal function as per the Acute Kidney Injury Network (AKIN) criteria [30], nor did any study report creatinine levels. Urine output at 24 hours was reported in five studies [22-25, 28] (**Table 4**). Three of the studies reported significantly increased urine output in the first 24 hours with invasive monitoring [23-25] while there was no difference in the Tokarik study [22]. In contrast Arlati (2006) [28] reported a lower urine output in the invasive monitoring group, however this result was not significant and this study employed a fluid restrictive protocol (**Table 4**). A meta-analysis of the five studies reporting urine output at 24 hours found a statistically significant difference between invasive monitoring compared to non-invasive controls (MD: 0.18, 95% CI: 0.03-0.34, P=0.02), but there was substantial heterogeneity (P=0.0001, I^2: 83%) (**Figure 2**).

Cardiac function

At least one measure of cardiac function was reported in all studies, with seven studies reporting cardiac index [21, 23-25, 27, 28]

Table 3. General characteristics of the study population

Author, year	Mean age (years)	Sex (% male)	Mean TBSA (%)	Injury Type	Fluid type used in first 24 hours	Mean Total volume over 24 hour (L)	Mean fluid rate in 24 hours (ml/kg/TBSA%)	Mean Total volume over 24 hour (L)	Mean fluid rate in 24 hours (ml/kg/TBSA%)
						I	C	I	C
Chen, 2017 [29]	I: 31.7 C: 33.0	N/R	I: 88.7±3.6 C: 86.1±6.2	N/R	Crystalloid Colloid	N/R	N/R	N/R	N/R
Soussi, 2016 [20]	46.9±6.5#	65%	42.5±8.1#	Inhalation	LR Albumin	N/R	N/R	N/R	N/R
Aboelatta, 2013 [27]	I: 30.4±15.2 C: 34.7±10.9	N/R	I: 41.1±10.9 C: 38.7±8.8	N/R	LR	16.3±5.4**	12.3±4.4	16.3±5.4**	12.3±4.4
Sánchez, 2013 [21]	48±18	74%	35.0±22.1	Inhalation Flame Electrical Other trauma	LR HES	N/R	NA	N/R	NA
Tokarik, 2013^ [22]	I: 48.5±13.9# C: 47±15.2#	N/R	I: 32.4±15.2# C: 35.5±16.1#	Inhalation	Crystalloid Colloid	6.8±0.8	9.7±1.4	6.8±0.8	9.7±1.4
Foldi, 2010 [23]	I: 52.9±16.0# C: 49.6±12.8#	80%	I: 45.9±8.7# C: 44.9± 9.9#	Flame	LR	N/R	N/R	N/R	N/R
Foldi, 2009 [24]	I: 52.5±18.4# C: 48.9±17.3#	81%	I: 40.1±10.7# C: 41.7±10.8#	Flame	LR	N/R	N/R	N/R	N/R
Csontos, 2008 [25]	48.6±6.8#	92%	I: 46±10# C: 41.8±10.1#	N/R	LR	N/R	N/R	N/R	N/R
Arlati, 2006 [28]	I: 40±14 C: 47±17	88%	I: 48±22 C: 49±22	Flame Explosion Other	LR HES	7.5±5.4*	12.0±4.7	7.5±5.4*	12.0±4.7
Holm, 2004 [26]	48.5±21.5#	76%	46.4±16.2#	Thermal Inhalation	LR	27.1† (12-44)	16.2† (8-33)	27.1† (12-44)	16.2† (8-33)

Mean age and %TBSA for Invasive monitoring and control presented; if not available, overall mean presented. ^From Erratum [39]. #Converted from Median (Interquartile range) to mean for comparison. †Presented as mean and (range). *P<0.05 compared to control group. **P<0.0001. C: control group, I: invasive monitoring group, N/R: Not reported, NA: Not applicable, HES = hydroxyethyl starch, LR: Lactated Ringers.

Table 4. Urine output recorded in first 24 hours

Author, year	UO (ml/kg/hr)		*p* value
	Invasive Monitoring	Control	
Tokarik, 2013 [22]	0.8±0.1	0.8±0.2	0.9
Foldi, 2010 [23]	1.1 (0.9-1.3)*	0.8 (0.6-1.1)*	<0.05
Foldi, 2009 [24]	1.1 (0.9-1.3)*	0.7 (0.5-1.1)*	<0.05
Csontos, 2008 [25]	1.1 (0.9-1.4)*	0.8 (0.6-1.0)*	0.0008
Arlati, 2006 [28]	1.0±0.4	1.3±0.6	NS

UO: urine output. Results reported as mean ± standard deviation or median (IQR)*.

(**Table 5**). Holm et al found a statistical difference in cardiac index at 24 hours between invasive and control groups ($P<0.05$), however exact values were unable to be determined from the available figure [26]. Aboelatta (2013) and Sánchez (2013) only reported mean cardiac indices for invasive monitoring of 2.9 and 3.22±1.12 L/min/m^2, respectively [21, 27]. Four studies remained for meta-analysis that found invasive monitoring groups had significantly higher cardiac index at 24 hr compared to non-invasive endpoints (MD: 0.65, 95% CI: 0.47-0.82, $P=0.00001$, $I^2=46\%$) (**Figure 3**).

Other measures of cardiac function were extracted however there was insufficient data to examine these indices including ITBVI and MAP across studies. Chen (2017) reported a MAP over the 48 hours study period and showed no difference between groups ($P<0.05$) [29]. Sánchez (2013) performed echocardiogram on hospital admission to determine the initial degree of volaemia, however this information was not stated to be part of the resuscitation protocol [21].

Abdominal compartment syndrome

Two studies reported values of intra-abdominal pressure (IAP) as an indicator of abdominal compartment syndrome. The single cohort study by Sánchez [21] reported intra-abdominal pressure from invasive monitoring to be 12.1±8.2 mmHg. The study by Tokarik [22] did not show a difference in IAP between the invasive monitoring and control groups (11.2±0.4 and 13.4±0.5 mmHg; $P=0.4$). Foldi (2010) reported no intra-abdominal compartment syndrome in either group, however no pressure values were given [23].

Blood lactate

Six studies in this series reported a lactate level at 24 hours [21, 23-26, 28]. Sánchez (2013) [21] reported a mean lactate of 2.45±1.78 mmol/L, with no control for comparison, leaving five studies for meta-analysis (**Table 6**). There was no statistical difference between lactate levels at 24 hours for invasive monitoring compared to groups using non-invasive endpoints (MD: -0.11, 95% CI: 0.44-0.22, $P=0.43$, $I^2=0\%$) (**Figure 4**).

Mortality and length of ICU stay

Eight studies reported mortality with the exception of Arlati et al, and Foldi (2009) which excluded patients that did not survive the first week (**Table 7**) [24, 28]. Soussi reported a 90-day mortality rate of 42% (28-day mortality was 26%), with all cases attributed to sepsis-related multiple organ failure [20]. Six studies were eligible for meta-analysis which found no significant difference in mortality between invasive monitoring and control groups (OR: 0.59, 95% CI: 0.29-1.18, $P=0.14$, $I^2=0\%$) (**Figure 5**). The mean length of ICU stay ranged from 24.6 to 44.5 days, with no differences between invasive monitoring and control groups (**Table 7**).

Discussion

This systematic review and meta-analysis has compared invasive monitoring against standard formulas to guide the acute resuscitation of major burns (>20% TBSA). Although organ function scores were inconsistently reported, significant improvements in the cardiac index and urine output were found when invasive monitoring was used compared to control groups applying non-invasive endpoints. An improved cardiac output is essential for all organ function, including renal function [31]. Mortality rates were lower in the invasive monitoring group compared with non-invasive controls, however, the difference did not reach statistical significance. Other measurements collected including lactate levels at 24 hours were similar in both groups, while abdominal compartment syndrome was under-reported.

One of the primary challenges in the acute resuscitation of burns is the balance between over- and under-resuscitation [8, 32]. Invasive monitoring can accurately assess the hemodynamic status of patients with burns, however the translation of invasive monitoring to improved outcomes of organ function in these

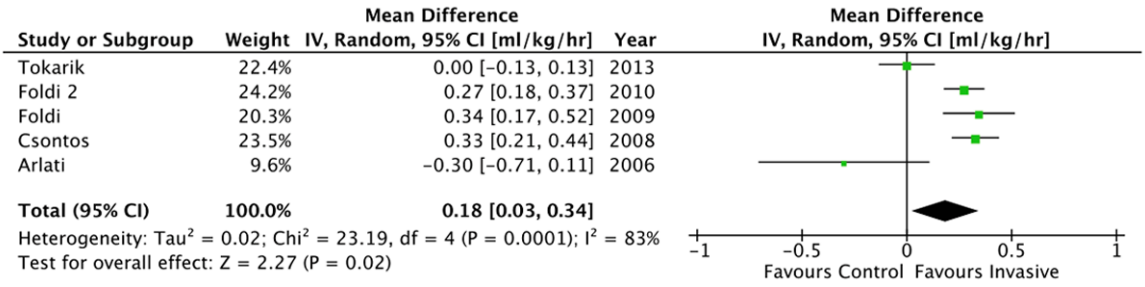

Figure 2. Urine output at 24 hours. CI: confidence interval. I^2: test of heterogeneity. The forest plot shows the mean difference calculated by the random effects model. Squares represent individual study effects and diamonds represent the summary effect from the meta-analysis. Horizontal bars represent 95% CIs and the vertical line in the MD plot is at 0, corresponding to the null hypothesis of no effect.

Table 5. Cardiac dysfunction measured at 24 hours

Author, year	Cardiac index (L/min/m²)		*p* value
	Invasive Monitoring	Control	
Aboelatta, 2013 [27]	2.9	Not stated	
Sánchez, 2013 [21]	3.22±1.12	No control	
Foldi, 2010 [23]	3.6 (3.3-3.9)*	2.8 (2.4-3.2)*	<0.05
Foldi, 2009 [24]	3.5 (3.2-3.9)*	2.9 (2.3-3.5)*	<0.05
Csontos, 2008 [25]	3.5 (3.3-3.8)*	3.0 (2.4-3.5)*	0.013
Arlati, 2006 [28]	3.4±0.7	3.1±0.7	NS

Results reported as mean ± standard deviation or median (IQR)*.

patients is mixed. All studies used different endpoints that included cardiac index, ITBVI, MAP and EVLWI, measured against traditional outcome measures, such as urine output. Our combined data suggest that there is limited evidence to date of the improvement in organ function or prevention of organ dysfunction in the first 24 hours as a result of invasive monitoring.

Although urine output was found to be significantly improved with invasive monitoring, this result must be interpreted with caution in the context of kidney dysfunction, as it does not necessarily reflect an acute kidney injury (AKI) [33]. This requires assessment of other renal parameters such as creatinine [34, 35]. The incidence of AKI in burn patients is as high as 43%, and therefore, this is a key area to target to improve patient outcomes [32, 33]. AKI in the acute setting can occur due to under-resuscitation and is associated with increased mortality [32, 33]. Measuring and reporting AKI during the acute phase post-burn better reflects the effects of under-resuscitation, whereas studies that report kidney function parameters at a later time point may reflect development of sepsis, multi-organ failure, fluid overload or the use of nephrotoxic drugs [36].

The strength of this review is that it presents a comprehensive overview of all reported multi-organ function measurements that have been investigated in the acute resuscitation of major burns when invasive monitoring has been compared to traditional endpoints. The included studies had primarily small sample sizes (<100 patients) and inconsistent reporting of organ function. Furthermore, many studies excluded severely burnt patients (>85% TBSA) and/or those not expected to live beyond 48 hours and thus were excluded from our review. It is highly recommended that this group of patients should not be excluded when evaluating resuscitation, and sub-analyses should be considered given the importance of tighter control of resuscitation for these patients [37]. The mechanism of injury is also an important parameter to differentiate, as patients with electrical injuries require greater volumes of fluid administration than do patients with thermal burns and should be included in a separate analysis [38].

In the current guidelines for resuscitation of major burns patients, urine output is used to titrate fluid requirement, however more studies are required to investigate the most accurate endpoint of resuscitation [9, 10]. As previously mentioned, urine output has not shown adequate evidence to protect organ function [12]. Another major gap in intensive care of patients with burns discovered in this review is the lack of standard invasive monitoring endpoints,

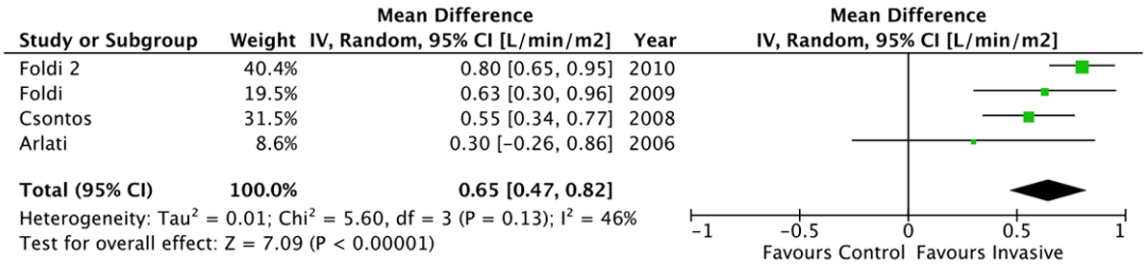

Figure 3. Cardiac index measured at 24 hours. CI: confidence interval. I^2: test of heterogeneity. The forest plot shows the mean difference calculated by the random effects model. Squares represent individual study effects and diamonds represent the summary effect from the meta-analysis. Horizontal bars represent 95% CIs and the vertical line in the MD plot is at 0, corresponding to the null hypothesis of no effect.

Table 6. Blood lactate levels at 24 hours

Author, year	Blood lactate (mmol/L)		*p* value
	Invasive monitoring	Control	
Sánchez, 2013 [21]	2.45±1.78	No comparison	
Foldi, 2010 [23]	2.3 (1.6-3.6)*	2.6 (1.5-3.7)*	NS
Foldi, 2009 [24]	2.3 (1.4-4.7)*	2.5 (1.6-3.5)*	NS
Csontos, 2008 [25]	2.3 (1.3-4.7)*	2.4 (1.7-3.6)*	NS
Arlati, 2006 [28]	1.97±1.24	3.23±2.25	NS
Holm, 2004 [26]	4.1±3.3	4.8±2.9	NS

Results reported as mean ± standard deviation or median (IQR)* NS: not significant.

which may have contributed to the heterogeneity found in the primary outcome measures.

Conclusion

Implications for practice

Currently, there is limited evidence on the benefits of invasive monitoring to guide fluid resuscitation in patients after severe burn trauma. Pooled data across multiple studies showed significant improvements in cardiac index and urine output when invasive monitoring was used compared to control groups. Further studies on the application of invasive monitoring in major burns patients may lead to improvements in patient outcomes as well as the establishment of evidence-based guidelines for goal-directed resuscitation using invasive monitoring. Multiple factors influence morbidity and mortality across lengthy hospital stays for major burns patients. For a more accurate understanding of the impact of resuscitation practices and organ function, studies need to measure and report organ function as a routine practice using validated metrics and measures in both the acute phase and long-term follow-up.

Implications for research

A clinically important question remains on whether invasive monitoring can improve the outcomes of major burns when used to guide fluid resuscitation. High-quality prospective randomised controlled trials are required to address this issue, that report early effects on organ function across all major burns patients. Future studies must implement appropriate randomisation methods, sample size and adequate blinding of clinicians to the outcome assessed. An ongoing challenge is having access to sufficient numbers of patients with similar burn injuries of different severities to accurately evaluate fluid resuscitation and the association with organ dysfunction. This could be achieved in a multi-centre trial involving a number of countries, as part of the data collection. Once more clinical information is obtained, there is also the question on whether implementation of new protocols can replace traditional formulas with careful titration by experienced healthcare staff.

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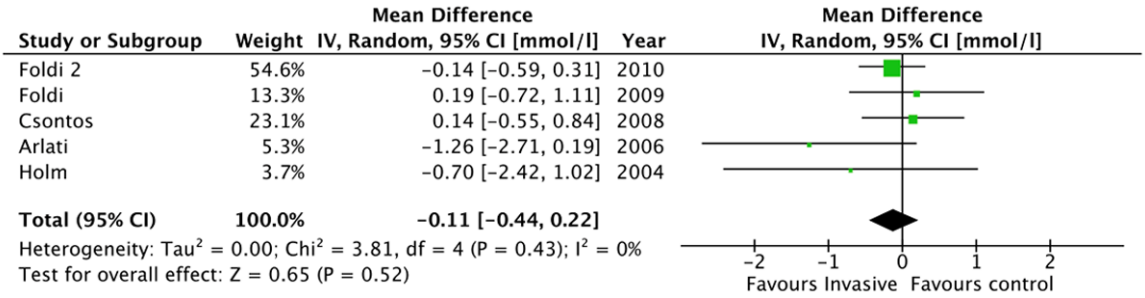

Figure 4. Mean difference and forest plot of blood lactate levels at 24 hours. CI: confidence interval. I^2: test of heterogeneity. The forest plot shows the mean difference calculated by the random effects model. Squares represent individual study effects and diamonds represent the summary effect from the meta-analysis. Horizontal bars represent 95% CIs and the vertical line in the MD plot is at 0, corresponding to the null hypothesis of no effect.

Table 7. Mortality and ICU admission

Author, year	Mortality (%)		*p* value	Length of ICU stay (days)		*p* value
	Invasive monitoring	Control		Invasive monitoring	Control	
Chen, 2017 [29]	7.69	14.28		NS		
Soussi, 2016 [20]	42	No control		34.8±9.4*		
Aboelatta, 2013 [27]	13.3	20	0.6	NS		
Sánchez, 2013 [21]	23	No control		27.1±21.8		
Tokarik, 2013 [22]	18	27	0.6	24.6±11.6	24.6±11.6	0.9
Foldi, 2010 [23]	20	33.33	NS	43.3±7.4*	44.5±6.4*	NS
Csontos, 2008 [25]	33.33	41.67	NS	27.3±5.3*	27.3±4.5*	NS
Holm, 2004 [26]	32	40	0.556	25*	23*	0.332

*Converted from Median (Interquartile range) to mean for comparison. NS: no significance.

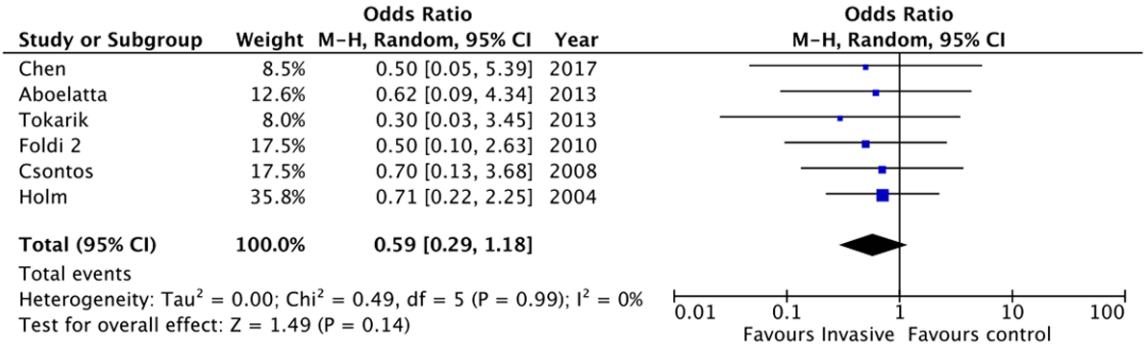

Figure 5. Mortality. CI: confidence interval. I^2: test of heterogeneity. The forest plot shows the odds ratio calculated by the random effects model. Squares represent individual study effects and diamonds represent the summary effect from the meta-analysis. Horizontal bars represent 95% CIs and the vertical line in the OR plot is at 1, corresponding to the null hypothesis of no effect.

Disclosure of conflict of interest

None.

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Appendix 1: Search strategies

MEDLINE and Embase search strategy using Ovid SP

'Burn'
'kidney failure' OR 'kidney' OR 'abdominal disease' OR 'multiple organ failure' OR 'organ dysfunction score' OR abdom* OR 'sequential organ failure assessment score' OR 'urine volume' OR 'gastric tonometry' OR 'acute kidney failure' OR 'bladder pressure' OR 'apache' OR 'cardiovascular disease' OR 'respiratory tract disease' OR 'lactate dehydrogenase'
'transesophageal echocardiography' OR 'TOE' OR 'echocardiography' OR 'hemodynamic monitoring' OR 'hemodynamics' OR 'cardiovascular monitoring device' OR 'cardiac output monitor'
'human'/de

Scopus search strategy

(TITLE-ABS-KEY (burn*) AND NOT TITLE-ABS-KEY ("burning sensation"))
("kidney" OR "abdom*" OR "organ failure" OR "MOF" OR "SOFA" OR "urine volume" OR "gastric tonometry" OR "AKI" OR "bladder*" OR "apache" OR "cardiac" OR "respiratory" OR "lactate")
"transesophageal echocardiography" OR "TOE" OR "echo*" OR "hemodynamic*" OR "ITBVI")
(LIMIT-TO (EXACTKEYWORD, "Human"))