Subclinical hypoperfusion in trauma patients and its influence on surgical fracture fixation: Systematic review and meta-analysis

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Abstract

Introduction
Subclinical hypoperfusion (SCH) is present when cellular hypoxia persists in the presence of normal vital signs. Its presence, as well as duration, is associated with poor patient outcomes. Different terminology and various definitions exist for SCH.

Methods
A systematic review was performed on the terminology and definitions used for SCH. Meta-analysis was performed on patients presenting with SCH. Primary study outcomes were mortality, ICU length of stay, and hospital length of stay. When surgical fracture fixation was performed, we compared the incidence of post-operative ventilation, respiratory complications and infective complications in SCH patients to patients without SCH.

Results
Eight observational studies were eligible for systematic review and meta-analysis. SCH is more commonly known as occult hypoperfusion, and lactate ≥ 2.5 mmol/L has been used most commonly to define hypoperfusion. Patients presenting with SCH had an increased mortality risk ratio of 4.02 (CI 2.62, 6.16). There was a non-significant increase in the standard mean difference for hospital length of stay for patients with SCH (1.21 days, 95% CI [−0.22, 2.64]). When haemodynamically stable trauma patients underwent surgical fracture fixation prior to correction of SCH they were at increased risk for post-operative ventilation (RR 2.54, 95% CI [1.56, 4.12]) as well as respiratory (OR 3.88, 95% CI [1.38, 10.89]) and infective complications (OR 5.54, 95% CI [2.02, 15.15]).

Conclusions
Trauma patients appearing haemodynamically stable should be screened for SCH, especially when early surgical fracture fixation is required.

Key words: subclinical hypoperfusion, occult, lactate, meta-analysis

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Background

The resuscitation of hypotensive trauma patients has traditionally been based on clinical markers such as heart rate and blood pressure. For the majority of patients this strategy is highly effective; however, recent studies have suggested that a subset of patients will present with normal heart rate and blood pressure while still having a substantially elevated lactate, indicative of cellular hypoxia.[1] This phenomenon has been termed subclinical or occult hypoperfusion (SCH) and its presence, as well as duration, is correlated with poor patient outcomes.[2-5] Recent publications have suggested that patients with subclinical hypoperfusion, who undergo surgery in this state, experience worse outcomes.[6,7]

In this study we aimed to: 1) investigate the terminology and definitions used for SCH; 2) undertake a systematic review and meta-analysis to determine the impact of SCH in haemodynamically stable trauma or polytrauma patients on the outcomes of mortality, intensive care unit (ICU) stay, and hospital stay; and 3) determine whether patients with SCH, who undergo surgical fracture fixation, experience a higher rate of serious intra- and post-operative complications.

Appendix 1.
Search strategy and databases

Database searches were conducted on 5 May 2013 using the OvidSP search engine (Ovid Technologies, Inc., New York, NY 2009) for the following databases:

1. EMBASE 1980 to 2013 Week 18
2. OVID Health Star (1966 to March 2013)
3. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and OVID MEDLINE(R) 1946 to May 5 2013
4. Cochrane Central Register of Controlled Trials (May 1 2013)
5. Cochrane Database of Systematic Reviews (May 1 2013)
6. ProQuest Dissertations and Theses A&I (May 1 2013)

Example of search conducted in OVID

	Search terms	
1.	occult hypoperfusion.mp.	78
2.	occult hypoperfusion.mp.	78
3.	subclinical hypoperfusion.mp.	4
4.	subclinical shock.mp.	2
5.	occult shock.mp.	34
6.	cellular shock.mp.	16
7.	cellular dysoxia.mp.	15
8.	2 or 3 or 4 or 5 or 6 or 7	148
9.	remove duplicates from 8	70

Methods

First, to identify the terminology and definitions used for SCH, we conducted a systematic review, identified all studies dealing with this concept, and presented the results in a narrative fashion. Second, to determine the impact of SCH in haemodynamically stable trauma or polytrauma patients, we extracted those studies that identified patients with SCH within a population of haemodynamically stable trauma patients. Using data from these studies we then conducted meta-analyses to examine the impact of SCH on the outcomes of mortality, ICU length of stay, and hospital length of stay. Third, to determine the impact of SCH on patients who subsequently underwent surgical fracture fixation, we compared the incidence of ventilatory requirement, respiratory complications, and infective complications in SCH patients who underwent surgery to those patients without SCH who underwent surgery.

Study eligibility

For this analysis we included all papers regardless of language, study design, sample size, publication status or date of publication. Studies were excluded if they were non-clinical or if they included septic patients. For inclusion, studies had to define haemodynamic stability using both blood pressure and heart rate.

Study identification

On 5 May 2013 we searched six databases (EMBASE, OVID Health Star, Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ProQuest Dissertations and Theses A&I), consulted with experts, reviewed reference lists from identified articles, and searched for cited references of key publications in Web of Science. The search terms and databases used are listed in *Appendix 1*. No language filters were used.

Eligibility assessment

The title and abstract of each citation was independently screened by both BG and RR to identify potentially eligible studies. If either reviewer felt the citation might contain a relevant study, the article was retrieved to undergo full text evaluation. Full texts of all citations identified as being potentially relevant were then independently evaluated by both BG and RR to determine eligibility. Disagreements were solved by consensus. Chance corrected inter-observer agreement for study eligibility was tested using kappa statistics.

Subclinical or occult hypoperfusion (SCH) and its presence, as well as duration, is correlated with poor patient outcomes

Table I: Varying definitions of subclinical hypoperfusion (SCH)

Study	Terminology	Definition of haemodynamic stability	Method of SCH diagnosis
Blow, 1999[2]	Occult hypoperfusion	SBP > 100 mmHg, Heart rate < 120 bpm, Urine output > 1 ml/kg/h	LA > 2.5 mmol/L
Claridge, 2000[3]	Occult hypoperfusion	SBP > 100 mmHg, Heart rate < 120 bpm, Urine output > 1 ml/kg/h	LA ≥ 2.5 mmol/L
Crowl, 2000[6]	Occult hypoperfusion	SBP > 100 mmHg, Heart rate < 120 bpm, Urine output > 1 ml/kg/h	LA ≥ 2.5 mmol/L
Schulman, 2004[27]	Occult hypoperfusion	N/A	LA ≥ 2.5 mmol/L
Ikossi, 2006[35]	Occult shock, Occult under-resuscitation	MAP ≥ 70 mmHg, Heart rate ≤ 110 bpm	PmO_2 ≤ 25 for at least 2 hours
Jansen, 2008[13]	Occult shock	SBP ≥ 100 mmHg	LA ≥ 3.5 mmol/L
Callaway, 2009[12]	Occult hypoperfusion	SBP ≥ 90 mmHg	LA ≥ 2.5 mmol/L or BD > 0 mEq/L
Martin, 2010[4]	Occult hypoperfusion	SBP ≥ 90 mmHg, Heart rate < 120 bpm	LA > 2.2 mmol/L or BD < −2 mEq/L
Thom, 2010[15]	Occult hypoperfusion	SBP ≥ 100 mmHg, Heart rate ≤ 110 bpm, Temperature > 35 °C	CI < 2.6 L/minute/m² or BE ≤ 3 mEq/L or SI ≥ 0.9 or ROPE ≥ 3.0
Corradi, 2011[16]	Occult haemorrhagic shock	SBP ≥ 90 mmHg, Urine output ≥ 30 ml/h LA ≤ 2 mmol/L No vasoactive drug support	SCH not identified Renal doppler RI used to predict haemorrhagic shock
Corradi, 2012[17]	Occult haemorrhagic shock	SBP ≥ 90 mmHg, No vasoactive drug support	SCH not identified Splenic doppler RI used to predict haemorrhagic shock
Grey, 2013[7]	Subclinical hypoperfusion	MAP ≥ 60 mmHg, Heart rate < 110 bpm	LA ≥ 2.5 mmol/L
Salottolo, 2013[5]	Occult hypoperfusion	SBP ≥ 90 mmHg, Heart rate < 120 bpm	Venous LA ≥ 2.5 mmol/L
Zakrison, 2013[14]	Occult shock	SBP > 100 mmHg, Heart rate < 110 bpm	BD ≥ 4 mmol/L

SBP = systolic blood pressure; MAP = mean arterial pressure; LA = lactate; BD = base deficit; BE = base excess; PmO_2 = Licox polarographic tissue oxygen monitor; CI = cardiac index; SI = shock index; ROPE = rate over pressure evaluation; RI = resistive index

Data collection and assessment of study quality

Data was extracted to an Excel spreadsheet recording: principle author, study design, total number of study patients, number of patients with SCH, number of patients without SCH, mortality, ICU length of stay, hospital length of stay, respiratory complications and infective complications. Authors were contacted to provide original patient data when it was insufficient for meta-analysis. Study quality was evaluated using the Newcastle Ottowa Scale.[8]

Statistical analysis

Meta-analysis was conducted using a random effects model in Review Manager Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Heterogeneity was assessed using I^2 and chi-squared analysis. Pooled dichotomous outcomes were reported as risk ratios (RR), odds ratios (OR) and 95% confidence intervals (CI). Continuous outcomes were reported as standard mean difference and 95% CI. We constructed a funnel plot to assess the possibility of publication bias.

Results

After having reviewed the results from our systematic review, in addition to articles identified in study reference and by experts, we present a narrative review of the terminology and definitions used for SCH.

When cellular hypoperfusion is present in patients with normal vital signs, a state of SCH exists. SCH has previously been referred to as occult hypoperfusion or occult shock and when caused by severe sepsis is commonly known as cryptic shock.[9] However, we believe SCH is a more appropriate term for this pathophysiological process as the hypoperfusion is not occult, but rather subclinical, and can easily be detected by the presence of raised lactate or base deficit. SCH has been well described in elderly trauma patients. This is due in part to the presence of medical comorbidities and the concurrent use of medications such as β-blockers that may mask the conventional signs of shock in these populations.[1,4,5,10–12] It has also been described in younger trauma patients when vital signs have been restored back to normal, but where persistent cellular hypoperfusion and oxygen debt remain.[1]

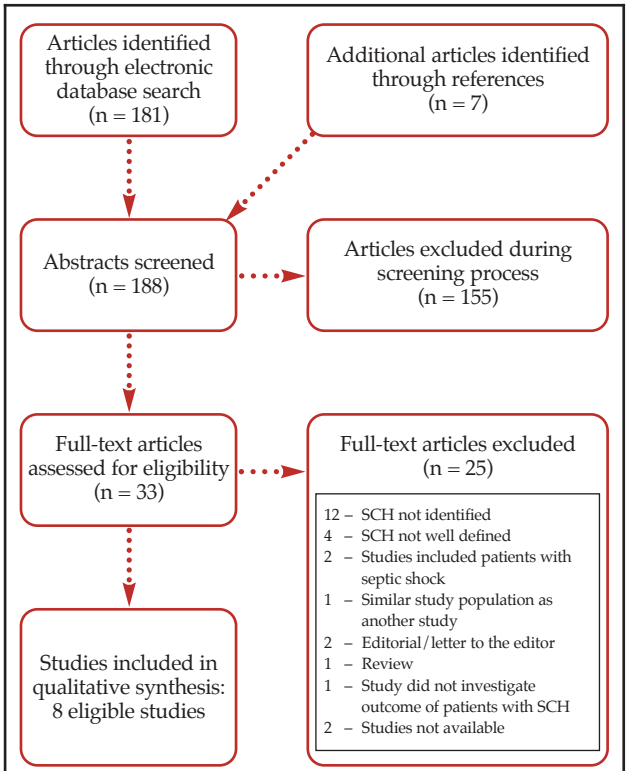

Figure 1. Study selection process
SCH = subclinical hypoperfusion

Various definitions and modalities have been used to define both haemodynamic stability and SCH (*Table I*). Haemodynamic stability definitions have generally included both systolic blood pressure (SBP) as well as heart rate while some have included mean blood pressure (MAP) and urine output in the definition. For the most part cellular hypoperfusion has been defined as a lactate ≥ 2.5 mmol/L but some studies have used a higher lactate threshold,[13] base deficit,[4,12,14] markers of impaired cardiac output[15] or organ hypoperfusion.[16,17]

To address our second objective we reviewed the 188 articles that met our search criteria (181 identified through the electronic database search; seven articles identified in references) and identified 33 articles for full text review. The chance corrected inter-observer agreement was excellent (kappa = 0.78). Of these 33 articles, 25 were excluded after full text review as: SCH was not identified in 12 studies;[10,16–26] four did not include vital signs or pulse rate in their definition of haemodynamic stability;[11–13,27] two included patients with sepsis;[28,29] the patient population in one study was similar to another study;[5,30] one study did not investigate the outcome of patients with SCH;[14] two citations were editorials or letters to the editor;[31,32] and one citation was a review article.[1] We were unable to obtain two articles as they did not provide correspondence details.[33,34]

In SCH, the hypoperfusion is subclinical, and can easily be detected by the presence of raised lactate or base deficit

Eight studies were therefore eligible for meta-analysis (*Figure 1*). These were all observational studies and their study quality and population characteristics are summarised in *Tables II and III*.

Seven of the eight studies included in the meta-analysis reported mortality, providing a total of 678 patients with SCH (*Figure 2*, supplementary data). Patients presenting with SCH had an increased mortality risk ratio of 4.02 (CI 2.62, 6.16). The pooled results were homogenous ($I^2 = 0\%$) and no publication bias was evident on the funnel plot (*Figure 3*, supplementary data).

Only four of the studies provided data for hospital length of stay (*Figure 4*, supplementary data). There was a non-significant increase in the standard mean difference for hospital length of stay for patients with SCH (1.21 days, 95% CI [−0.22, 2.64]) and this result showed considerable heterogeneity (I^2 = 99%). Insufficient data were available to analyse ICU length of stay as it was only reported on by two articles.[3,4]

Table II. Newcastle-Ottawa Scale assessment of study quality[8]

Study	Study design	Selection of study group (maximum = 4 stars)	Comparability of groups (maximum = 2 stars)	Ascertainment of outcome (maximum = 3 stars)
Blow[2]	Retrospective cohort	★★★★	★★	★★★
Claridge[3]	Prospective cohort	★★★★	★	★★★
Crowl[6]	Retrospective cohort	★★★	★★	★★★
Ikossi[35]	Prospective cohort	★★★★	Nil	★★★
Martin[4]	Retrospective cohort	★★	★	★★★
Thom[15]	Prospective cohort	★★★★	★	★★★
Grey[7]	Retrospective cohort	★★★	★★	★★★
Salottolo[5]	Retrospective cohort	★★	★★	★★★

Table III. Study characteristics

Study	Population	Total population of stable patients (mean, SD)			SCH patients (mean, SD)			No SCH (mean, SD)	
		Size (n)	Age	ISS	Size (n, %)	Age	ISS	Age	ISS
Blow, 1999[2]	Polytrauma patients: ISS ≥ 20	79	43 (19)	28 (6.4)	58 (73.4)	44.7 (19.9)	29.2 (6.1)	42 (14.6)	26 (4.2)
Claridge, 2000[3]	Trauma patients admitted to ICU	364	43.7 (2.0)	23.8 (1.1)	246 (67.6)	43.2 (2.1)	24.9 (1.2)	45.1 (1.9)	20.3 (1)
Crowl, 2000[6]	Trauma patients with femur fractures fixed < 24 hours	47	N/A	19.21 (8.2)	20 (42.6)	N/A	21 (10.66)	N/A	17.42 (6.34)
Ikossi, 2006[35]	Trauma patients admitted to ICU, AIS ≥ 3 in any body region	14	40 (18)	N/A	4 (28.6)	N/A	N/A	N/A	29 (10)
Martin, 2010[4]	Geriatric trauma patients > 65 years	72	N/A	8.18	28 (38.9)	N/A	10.5	N/A	6.7
Thom, 2010[15]	Polytrauma patients: ISS > 15 or significant injury to ≥ two body regions	62	52 (21)	19 (11)	7 (11.3)	58 (20)	29 (9)	49 (21)	17.7 (11.3)
Grey, 2013[7]	Polytrauma patients: NISS > 16	36	35.8 (14.9)	24.67 (10.871)	19 (52.8)	37.3 (15.37)	32.1 (8.42)*	34.2 (14.37)	28 (9.55)*
Salottolo, 2013[5]	Geriatric trauma patients ≥ 65 years	1416	79	9	300 (21.2)	N/A	N/A	N/A	N/A

ISS = injury severity score; AIS = abbreviated injury scale; *NISS = new injury severity score

For our third objective we identified only two studies that investigated outcomes in patients undergoing surgical fracture fixation in the presence of SCH.[6,7] Crowl *et al*. reported on the incidence of post-operative complications among patients with SCH undergoing intramedullary nailing of femur fractures in the first 24 hours post admission.[6] Different systemic complications were noted, including respiratory, cardiac, haematologic, neurologic, gastrointestinal, musculoskeletal and infectious. Patients with SCH had significantly more post-operative complications. Thirty-five complications were encountered in the 20 patients with SCH, compared with 11 complications in the control group of 27 patients. Ventilation requirement was also reported. Thirteen patients with SCH required ventilation, compared with only five patients from the control group.

The study by Grey *et al*. reported on the outcome of polytrauma patients with SCH undergoing early surgical fracture stabilisation.[7] Their primary findings were higher inotrope requirements in the first 24 hours post-operatively ($p = 0.02$) and higher sequential organ failure assessment (SOFA) scores on day three ($p = 0.003$) in the SCH group. For the purposes of this meta-analysis the original data from Grey's study were used to investigate the outcomes of ventilation requirement, respiratory complications and infective complications.

When haemodynamically stable trauma patients underwent surgical fracture fixation prior to correction of SCH they had an increased likelihood for ventilation post-operatively (RR 2.54, 95% CI [1.56, 4.12]) and a higher incidence of respiratory (OR 3.88, 95% CI [1.38, 10.89]) and infective complications (OR 5.54, 95% CI [2.02, 15.15]) (*Figures 5–7*, supplementary data).

Discussion

Statement of principle findings

First, our systematic review of the literature identified a wide range of definitions for SCH, the majority of which included a lactate measurement ≥ 2.5 mmol/L in the presence of normal haemodynamic parameters (*Table I*). Secondly, meta-analysis found patients with SCH were at increased risk of mortality (RR 4.02; 95% CI 2.62–6.16; $I^2 = 0\%$) and showed a non-significant increase in hospital length of stay (mean difference 1.21 days; 95% CI −0.22–2.64; $I^2 = 99\%$). Finally, patients with SCH who underwent surgical fracture fixation within the first 24 hours of presentation required more ventilation (RR 2.54, 95% CI 1.56–4.12; $I^2 = 0\%$), and were at a higher risk of respiratory (OR 3.88, 95% CI 1.38–10.89; $I^2 = 0\%$) and infective complications (5.54, 95% CI 2.02–15.15, $I^2 = 0\%$).

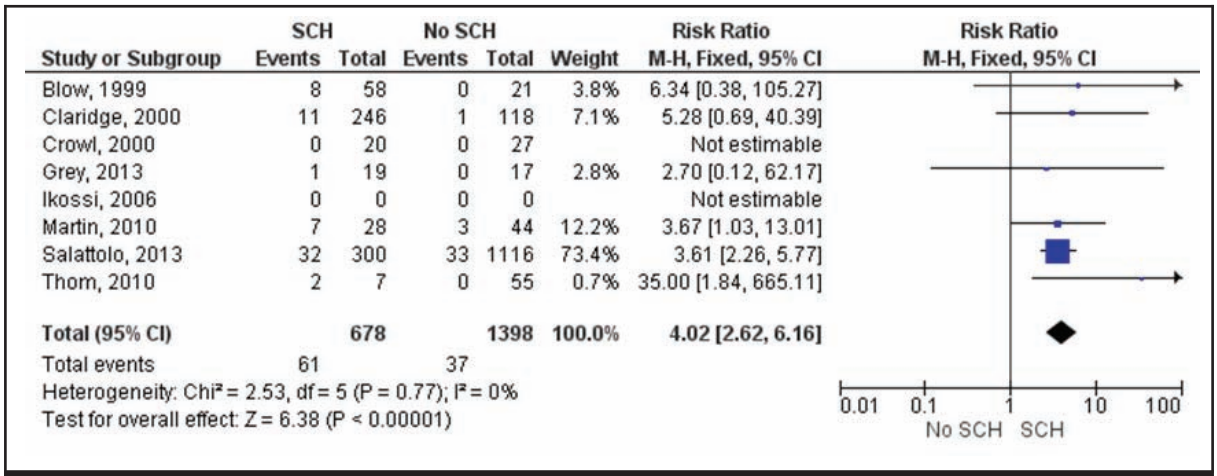

Figure 2. Forest plot comparing risk ratios for mortality in patients presenting with subclinical hypoperfusion (SCH)
M–H = Mantel–Haenszel; CI = confidence interval

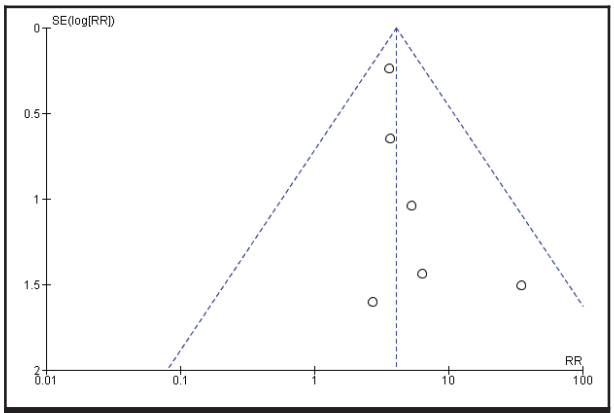

Figure 3. Funnel plot showing distribution of treatment effect of studies investigating mortality in patients presenting with SCH

These studies were all of good quality as measured by the Newcastle–Ottowa Scale

Strengths and weakness of this review

There were several limitations to this meta-analysis. There has been very little published on SCH and the eight studies included in the meta-analysis were all observational studies. However, these studies were all of good quality as measured by the Newcastle–Ottowa Scale (*Table II*). The study populations in the eight papers were all trauma patients with variable injury severity and age groups. Three papers investigated SCH in polytrauma patients[2,7,15] and different definitions of polytrauma were used; Blow *et al*. defined polytrauma as ISS > 20; Thom *et al*. defined polytrauma as ISS > 15 or significant injury to two or more body regions; and Grey *et al*. used the New Injury Severity Score (NISS) > 16 to define polytrauma. Two papers included trauma patients admitted to intensive care units but did not score the injury severity.[3,35] The study by Crowl *et al*. investigated trauma patients with femur fractures that were fixed with intramedullary nails within the first 24 hours.[6] Twelve out of the 20 patients with SCH had ISS > 18. Two studies focused on SCH in the elderly (> 65 years) trauma population but did not select patients based upon their ISS.[4,5] Only two studies with small patient numbers were available for the third objective of this meta-analysis to determine the impact of SCH on trauma patients going for surgical fracture fixation.[6,7]

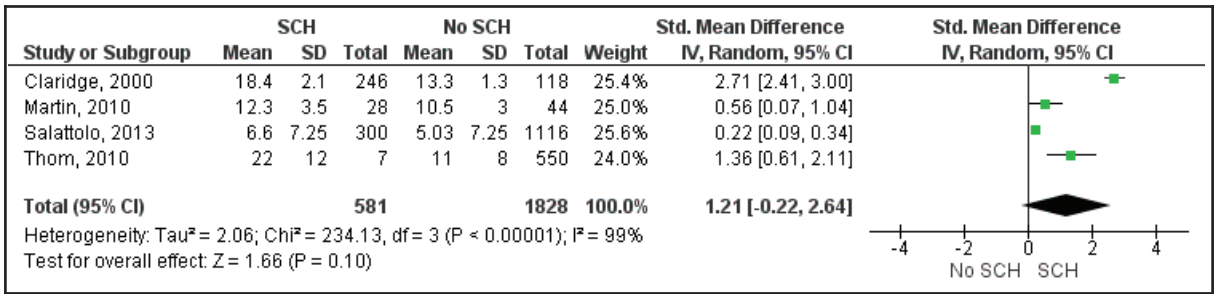

Figure 4. Forest plot comparing standard mean difference in hospital length of stay in days for patients presenting with subclinical hypoperfusion (SCH)
CI = confidence interval

Interpretation and implication of findings

This analysis highlights a few key points with regard to SCH in the trauma population. Various definitions have been used to describe haemodynamic stability and SCH (*Table I*).

Our study emphasises the use of cellular hypoperfusion markers rather than traditional vital signs in the assessment of shock and resuscitation

The target systolic blood pressure and mean arterial pressure in trauma patients is debatable, and is influenced by the patient's age, cardiovascular conditioning and other medical comorbidities. The systolic blood pressures or mean arterial pressures used in the included studies were adequate in selecting clinically apparent haemodynamically stable patients, provided the pulse rate was also normal. To allow for the normal sympathetic response to trauma and pain, the maximum heart rate used to define haemodynamic stability in all the studies was either 110 or 120 beats per minute. Our study emphasises the use of cellular hypoperfusion markers rather than traditional vital signs in the assessment of shock and resuscitation.

The most common marker used to identify SCH was lactate. Most authors chose a minimum value of 2.5 mmol/L to define cellular hypoperfusion. In the presence of normal vital signs this was accurate in identifying SCH. More direct ways to detect hypoperfusion have been investigated such as the Licox polarographic tissue oxygen monitor that measures partial pressure of oxygen in deltoid muscle[35] as well as renal – and splenic Doppler resistive indices.[16,17] These indices should be investigated further as possible markers for SCH.

This study affirms other studies that show that trauma patients presenting with SCH have worse outcomes. Even though these patients appeared haemodynamically stable, they still had a four-fold higher mortality than patients without SCH. All trauma patients and especially polytrauma patients need to be screened for SCH by having lactate or base deficit measured. A recent survey among Canadian traumatologists revealed that even though 78% of respondents were aware of SCH, only 8% were screening for SCH.[36] A further 88% felt that they should be screening for SCH.

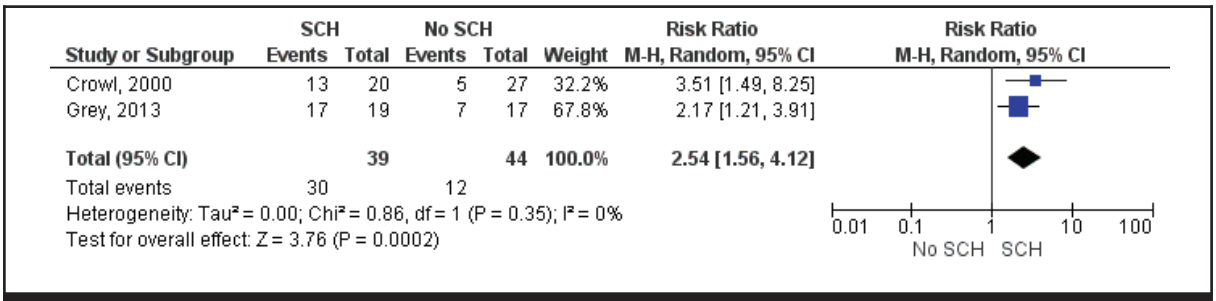

Figure 5. Forest plot comparing ventilation requirement for patients with SCH undergoing surgery
M–H = Mantel–Haenszel; CI = confidence interval

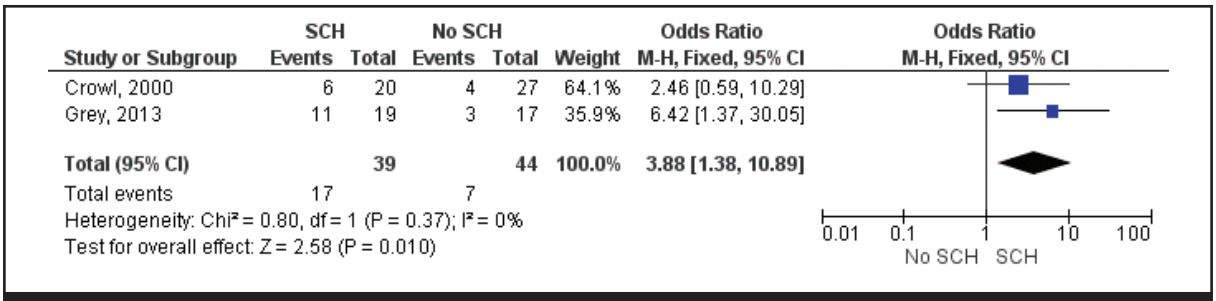

Figure 6. Forest plot comparing the incidence of respiratory complications among patients with SCH undergoing surgery
M–H = Mantel–Haenszel; CI = confidence interval

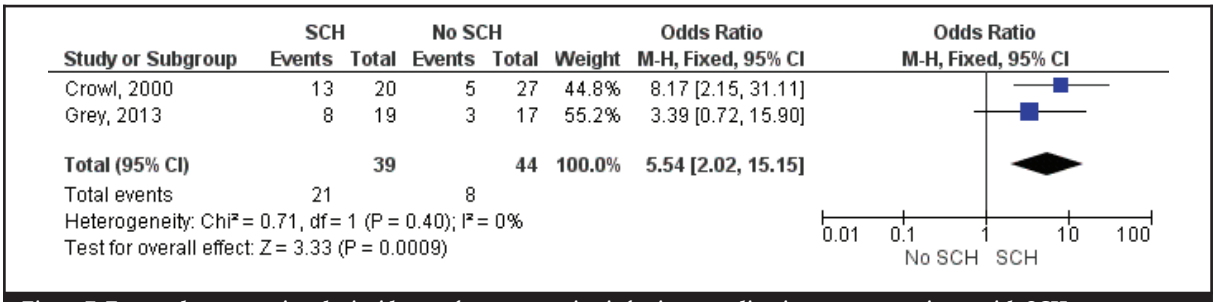

Figure 7. Forest plot comparing the incidence of post-operative infective complications among patients with SCH
M–H = Mantel–Haenszel; CI = confidence interval

Our study also showed that surgical fracture fixation in the presence of SCH was associated with increased perioperative morbidity. Even though only two studies with small patient numbers were available for this part of the meta-analysis, both studies were of good quality. Both these studies investigated fracture fixation in the presence of SCH. The timing and the type of fracture fixation in the trauma patient is influenced by the haemodynamic state of the patient. Early definitive fracture fixation, also known as 'early total care', has been advocated in haemodynamically stable polytrauma patients.[37–39] This has been shown to reduce fat embolism syndrome (FES), acute respiratory distress syndrome (ARDS), pneumonia and ICU length of stay. We advocate delaying early definitive fracture fixation in haemodynamically stable trauma patients with SCH until resuscitation is complete. While aiming to do early definitive fixation in the first 24 hours, O'Toole *et al*. safely delayed femoral nailing in polytrauma patients (ISS > 17) until resuscitation was complete as evidenced by a normalising lactate.[40] Femoral nailing started more than 8 hours after admission to theatre in 48% of their patients and this approach was associated with an ARDS rate of 1.5% and a mortality rate of 2%.

Future research

Very little research has been done into SCH and no randomised controlled trials have been conducted on the subject. We know that both the presence of SCH and surgery in the presence of SCH is detrimental, but prospective randomised controlled trials are required to prove that patients presenting with SCH have improved outcomes when surgery is delayed until lactate normalises.

Conclusion

SCH is most commonly defined as serum lactate ≥ 2.5 mmol/L in the presence of normal vital signs. The presence of SCH in clinically stable trauma patients was associated with a four-fold increase in mortality risk as well as a non-significant increase in hospital length of stay. Trauma patients should therefore be screened for SCH. Trauma patients who underwent surgical fracture fixation in the presence of SCH required more ventilation and were at a higher risk of respiratory and infective complications. When possible, fracture fixation should be delayed until SCH is corrected. Prospective randomised controlled trials are needed to investigate this further.

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