Use of methylene blue in sepsis: a systematic review
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CRD summary
The authors concluded that methylene blue increases vascular resistance and mean arterial pressure in patients with septic shock, but the effects on mortality and oxygen delivery are unknown and further research is required. In view of the limited evidence, incomplete reporting of review methods and lack of a study quality assessment, it is not possible to confirm the reliability of these conclusions.

Authors' objectives
To evaluate the effects of methylene blue (MB) on haemodynamic status and other outcomes in patients with septic shock.

Searching
MEDLINE (1996 to July 2005), EMBASE (1980 to July 2005) and the Cochrane CENTRAL Register (Issue 3, 2005) were searched using the reported search terms. References from the included studies were also checked.

Study selection
Study designs of evaluations included in the review
Controlled trials, case reports and case series were eligible for inclusion in the review. The included studies were randomised controlled trials (RCTs), case series and case reports.

Specific interventions included in the review
Studies that evaluated MB were eligible for inclusion. The controlled studies evaluated different MB regimens and compared these regimens with an isotonic saline control; one controlled study administered vasopressors before MB, the other did not. The MB regimens evaluated were a 2 mg/kg bolus over 15 minutes followed by infusion at increasing rates from 0.25 to 2 mg/hour, and a 0.5 mg/kg per hour infusion over 6 hours. The observational studies also used different MB regimens; most used boluses of 1 to 4 mg/kg over 10 to 60 minutes.

Participants included in the review
Studies of patients aged 16 years or older with any of the following conditions were eligible for inclusion: sepsis defined as the presence of a systemic inflammatory response syndrome with demonstrated infection; septic shock defined by hypotension (systolic blood pressure <90 mmHg), and signs of tissue hypoperfusion (oliguria, arterial lactate >2.5 mmol/L); refractory septic shock (arterial hypotension persisting despite fluid administration and concurrent intravenous infusion of two or more vasoactive drugs for 1 hour).

Outcomes assessed in the review
Studies reporting haemodynamic variables or mortality rates were eligible for inclusion. The following outcomes were reported in the review: mean arterial pressure, mean pulmonary artery pressure, pulmonary vascular resistance, systemic vascular resistance, stroke volume, left-ventricular stroke work indices, oxygen delivery, requirements for vasopressors, survival rates at 28 days and adverse effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and agreed on the eligibility of all of the included studies.

Assessment of study quality
The authors did not state that they assessed validity. However, they did note the study designs.

Data extraction
The data were extracted onto a standardised form, but the authors did not state how many reviewers performed the data extraction. For each study, significant outcomes were listed.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
The studies were grouped by study design.

Results of the review
Thirteen studies (n=133) were included: 2 RCTs (n=50) and 11 case series and case reports (n=83; sample size range: 1 to 15).

RCTs.

One RCT (n=20; haemodynamic variables assessed at 24 hours) reported increased mean arterial pressure and maintenance of stroke volume and left-ventricular stroke work indices in patients who received MB. Oxygen delivery was unchanged in the MB group but decreased in the control group. Patients receiving MB had reduced requirements for norepinephrine, epinephrine and dopamine. There was no statistically significant difference in survival rates at 28 days in the MB group compared with the control group (50% versus 30%, p-value not reported). No adverse effects were reported.

One RCT (n=50; mean arterial pressure and heart rate measured at 24 and 48 hours) reported that mean arterial pressure was significantly increased in the MB group compared with the control group. No significant adverse effects were reported.

Observational studies.

All of the observational studies that assessed mean arterial pressure (11 studies) and/or systemic vascular resistance (7 studies) reported a significant increase in patients receiving MB. Three studies reported a significant reduction in the requirement for vasopressors. Five studies reported an increase in mean pulmonary artery pressure or pulmonary vascular resistance.

Authors’ conclusions
MB increases systemic vascular resistance and mean arterial pressure in patients with septic shock, but its effects on mortality and oxygen delivery are unknown and further research is required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Inclusion criteria for the outcomes were broad, which gives rise to the potential for selective reporting of outcomes. Given the paucity of identified studies, the broad inclusion criteria for study design seemed appropriate. Several relevant sources were searched but it was unclear whether any attempts were made to minimise publication bias and language bias, thus other relevant studies might have been omitted. Methods were used to minimise reviewer error and bias in the selection of studies, but it was unclear whether similar steps were taken for the extraction of data. The review did not include an assessment of study validity, which means that the likely reliability and validity of the results from these studies cannot be determined and, consequently, the data synthesis may not be reliable.

The narrative synthesis, with studies grouped by design, was appropriate given the few and diverse studies identified. Results data were not reported, so it is not possible to verify findings reported in the review. In view of the limited evidence from two small RCTs of unknown quality plus a number of potentially biased observational studies, and incomplete reporting of review methods, it is not possible to confirm the reliability of these conclusions. The need for further research appears to be supported.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that more RCTs are required to evaluate the role of MB in patients with septic shock.

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