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A systematic review of goal directed fluid therapy: Rating of evidence for goals and monitoring methods☆

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ABSTRACT

Purpose: To review the literature on goal directed fluid therapy and evaluate the quality of evidence for each combination of goal and monitoring method.
Materials and Methods: A search of major digital databases and hand search of references was conducted. All studies assessing the clinical utility of a specific fluid therapy goal or set of goals using any monitoring method were included. Data was extracted using a pre-determined *pro forma* and papers were evaluated using GRADE principles to assess evidence quality.
Results: Eighty-one papers met the inclusion criteria, investigating 31 goals and 22 methods for monitoring fluid therapy in 13052 patients. In total there were 118 different goal/method combinations. Goals with high evidence quality were central venous lactate and stroke volume index. Goals with moderate quality evidence were sublingual microcirculation flow, the oxygen extraction ratio, cardiac index, cardiac output, and SVC collapsibility index.
Conclusions: This review has highlighted the plethora of goals and methods for monitoring fluid therapy. Strikingly, there is scant high quality evidence, in particular for non-invasive G/M combinations in non-operative and non-intensive care settings. There is an urgent need to address this research gap, which will be helped by methodologies to compare utility of G/M combinations.

1. Introduction

Almost 40 years ago, Shoemaker and colleagues published a landmark study introducing the use of physiological goals to guide fluid therapy [1]. They demonstrated that mortality could be reduced by titrating fluid therapy to pre-determined cardiorespiratory variables. This was the birth of 'goal directed fluid therapy' (GDFT).

Since then many goals have been promoted to direct fluid therapy, both invasive and non-invasive [2]. Despite evidence demonstrating the potential benefit of GDFT in a number of disease states [3], there remains no consensus about the most effective goals for fluid therapy or the most appropriate monitoring methods. As such, GDFT remains a well-accepted concept that has not yet translated to an established standard of care. Formal evaluation of the different goal/method (G/M) combinations for GDFT has been hampered by the many different goals, the number of methods to monitor fluid therapy, the variation in study design, and the lack of comparable controls. A new approach to evaluating G/M combinations is required so that the leading options can be formally studied to establish an evidence based standard of care for GDFT.

The aim of this study was to conduct a systematic review of the literature and evaluate the quality of evidence for each G/M combination using the established GRADE methodology [4–9].

2. Materials and methods

2.1. Literature search

A systematic and comprehensive search of major reference databases (PubMed, MEDLINE, Embase, and the Cochrane Library) was undertaken with no constraint on publication date (all available entries to Feb 2013 were searched) or language using the search string: "(fluid and (goal-directed or endpoint)).mp. [mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]". The reference lists of articles selected for inclusion as well as all relevant review articles were hand searched to ensure inclusion of all relevant studies.

2.2. Inclusion and exclusion criteria

Articles were assessed for inclusion by 2 reviewers (HW and MH). All laboratory studies, observational studies and clinical trials that directly

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assessed the efficacy of a specific fluid therapy goal or set of goals in combination were identified. Randomized controlled trials (RCTs), cohort studies, case control studies, case series and historical control studies were all included. Review papers were excluded (although their reference lists were hand searched) as well as any papers that did not investigate the benefits of at least one goal for fluid therapy. The concurrent use of inotropes and vasopressors was permitted.

2.3. Data extraction

Four authors (HW, MH, MV and MD) were involved in data extraction and checking the data for accuracy, which was done using a pre-defined *pro forma*. The data fields in the template included title, authors, date of publication, study type, setting, participant numbers, participant description, goal(s) assessed, outcomes assessed, exposure and comparison interventions, outcomes and precision of outcomes.

2.4. Data definitions

The term *fluid therapy* included any form of intravenous fluid encompassing resuscitation, maintenance, replacement and nutrition fluid therapy. The publications were identified as human or animal studies. As each goal could be measured by several different methods, and thus there could be several G/M combinations. The methodology used to measure each goal was further categorized as invasive or non-invasive. Invasive was defined as requiring a monitoring method that involved puncture of the skin (excluding peripheral venous blood sampling), use of an indwelling catheter or an endoscope. Invasive methods were further subdivided into those that required the patient to be ventilated or those that could be used in non-ventilated patients. Non-invasive techniques were defined as those that were monitored by an entirely external methodology.

2.5. Rating the quality of evidence

The body of evidence from clinical studies supporting each G/M combination was assessed using the GRADE methodology [4–9]. The GRADE method identifies several qualities that either decrease or increase the quality of a body of evidence. The factors decreasing evidence quality are poor study design (for example observational studies rather than RCTs), study bias (for example, an RCT with inadequate blinding), inconsistency of results between studies (if more than 33% of studies investigating a particular G/M combination are found to have opposing findings), indirectness of measures (if a secondary measure is used to proxy for a main study outcome), imprecision in outcome measurement and publication bias. Factors increasing evidence quality include; a large intervention effect, the presence of a dose response gradient and when confounding variables are present that would likely cause a conservative estimate of the true effect.

Each clinical paper was evaluated in the same fashion as done by the GRADEPro software [10] and all factors were included excepting the presence of a dose response gradient as this was deemed not applicable to the outcomes assessed in our sample of papers. The reason for this being that the outcomes investigated are not consistently reported as continuous variables and therefore it is not possible to demonstrate a dose–response gradient. The rating rubric used is shown in Table 1. In line with the GRADE method, an evidence score of ≥ 1 equates to high quality evidence, 0 equates to moderate quality, -1 equates to low quality and ≤ -2 equates to very low quality.

Table 1
Rating of evidence quality and usefulness

Factor	Descriptors
Study design	+1 Paper is an RCT
	−1 Paper is an observational study
	0 Negligible limitations likely to cause biases in the body of evidence
Study bias	−1 Serious limitations likely to cause biases in the body of evidence
	−2 Very serious limitations likely to cause biases in the body of evidence
	+1 Paper finds benefit by targeting goal
Inconsistency	0 Paper finds no benefit by targeting goal
	−1 Paper finds harm done by targeting goal
	0 Negligible doubts about directness of measures used in body of evidence
Indirectness	−1 Serious doubts about directness of measures used in body of evidence
	−2 Very serious doubts about directness of measures used in body of evidence
	0 No significant result, or significant results have clinically significant CI margins
Imprecision	−1 Some key significant results with questionably clinically significant CI margins
	−2 Significant results with no clinically significant CI margins
	0 No evidence of publication bias for body of evidence (peer reviewed journal)
Publication bias	−1 High probability of publication bias (non peer reviewed journal)
	−2 Very high probability of bias (known previous non publication of results)
Large effect	+2 Relative risk ratio >5 or <0.20
	+1 Relative Risk Ratio 2-5 or 0.5-0.2
	0 = Relative Risk Ratio 0.5-2 or not presented in paper/not calculable
Bias causing conservatism	+1 All possible biases are likely to cause conservative estimation of effects
	0 All possible biases are not likely to have this effect.

3. Results

3.1. Data overview

A total of 1118 articles published between 1984 and 2013 were identified by the initial literature search. The inclusion and exclusion of studies is summarized in Fig. 1. A total of 81 studies were included. These included six laboratory studies (Supplementary Table 1) and 75 clinical studies comprising 13,052 patients. Of the 81 studies, 42 were obtained by hand searching reference lists. The entire sample of studies investigated 31 unique goals, and 22 methods of monitoring to give a total of 118 G/M combinations. Of these combinations, 96 were invasive and 22 non-invasive. Table 2 shows the 108 different combinations of goals and methods for monitoring fluid therapy evaluated by the 75 clinical studies. Three G/M combinations were only investigated by laboratory studies and as a result are not included in Table 2. The 6 laboratory studies investigated 10 G/M combinations between them (see Supplementary Table 1). The most frequently investigated goal for monitoring fluid therapy was stroke volume as determined by oesophageal Doppler ($n = 14$).

3.2. Clinical endpoints

The studies covered a large number of different clinical endpoints making quantitative analysis (i.e. a meta analysis) impossible. Studies generally investigated either clinical endpoints or the accuracy of measurement of a specific G/M combination.

3.3. Rating the evidence around goals and methods of monitoring fluid therapy

Fig. 2 shows a breakdown of the evidence quality behind the 108 G/M combinations from the clinical studies. The most striking finding is that very little high quality evidence exists in any category. Table 2 further subdivides clinical studies into individual G/M combinations within the non-invasive, invasive non-ventilated and