

## Hidden Truths in Medical Research. What We Need to Know from Meta-Analyses and Why We Need to Be Careful? A Paradigm from Goal-Directed Fluid Therapy in Clinical Practice

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Received: 01 August 2018

Published: 03 August 2018

**Keywords:** *Clinical Practice; Fluid Therapy; Therapeutic Strategy*

Throughout the last century investigators have studied and debated the usefulness of many pharmacological and non-pharmacological interventions in medical practice. In time our knowledge of evidence based medicine has grown, but translating this amount of information in complex systems is not effortless [1].

For instance, in our anesthetic practice the use of goal-directed fluid therapy (GDFT) during elective surgery has been at first enthusiastically promoted and thereafter strongly debated. Most recent Randomized Controlled Trials (RCTs) have shown that individualized administration of fluids has been associated with improved perioperative outcome. However, earlier evidence had partially denied this as some studies, indeed very few, comparing personalized fluid therapy with protocolized fluid administration strategies failed to confirm a survival benefit [2-5]. Although many of those studies were underpowered, medical literature produced very scant correspondence on this issue, and thus they have been arbitrarily included in meta-analytic reviews. Hence, results from meta-analyses have worsened the already poor trust in GDFT and have exacerbated the split between supporters and deniers of this practice [6-8].

Indeed, aside from any clinical standpoint, the question that should be raised is whether positive publication bias and publications of underpowered studies might have influenced the diffuse opinion that GDFT is still not an evidence based effective therapeutic strategy and that it needs further research. In fact, many RCTs

have shown that GDFT is beneficial, however when investigators tried to pool those results using meta-analysis and meta-regression models they concluded that there is questionable benefit over a standard fluid restriction in terms of postoperative mortality, while risk reduction of perioperative morbidity has received general consent [8]. But why a beneficial strategy should reduce in-hospital morbidity having no effect at all on 30-days mortality, when it is undisputed that most common fluid related postoperative complications do increase mortality? Once again logic does not come to our aid.

The fact is that meta-analyses are strongly biased by positive publication bias and inclusion of underpowered studies. Albeit the issue of positive publication bias has been somehow addressed in medical literature and some unfolding has been proposed in current medical meta-analytic standards, inclusion of underpowered studies remains a common and undebated very strong bias. Usually power analysis is not addressed in meta-analytic experimental design and RCTs are not weighted in terms of their potential beta error. But it is not a case that historically Cohen dedicated an entire statistical dissertation on the type II error [9]. And indeed it has been shown that underpowering strongly affects medical literature. In fact, studying 14,886 meta-analyses, Turner *et al.* could demonstrate that 70% of all included studies were underpowered. Odds ratios in underpowered studies were 15% lower than in adequately powered studies ( $p < 0.0001$ ) in meta-analyses of controlled pharmacological trials, whilst they were 12% lower in meta-analyses of non-pharmacological trials. Most interestingly, the standard error of the intervention effect increased by a median of 11% (interquartile range from -1% to 35%) when underpowered studies were omitted and between study heterogeneity tended to decrease [10].

In conclusion, can we be so convinced that GDFT is not effective? And most importantly, can we ethically avoid to implement those therapies because meta-analyses tell us that they are still not definitely effective?

An answer to this big question should be given by our scientific community. However, it is still lacking and maybe it will remain so far in the future.

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Michele Claudio Vassallo (2018). Hidden Truths in Medical Research. What We Need to Know from Meta-Analyses and Why We Need to Be Careful? A Paradigm from Goal-Directed Fluid Therapy in Clinical Practice. *CPQ Anaesthesia and Pain Management*, 1(1), 01-03.

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