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A Systematic Review and Meta-Analysis of Intraoperative Goal Directed Fluid and Haemodynamic Therapy in Children and Postoperative Outcome

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Abstract

Introduction: In adults, studies have shown that when goal directed fluid and haemodynamic therapy was applied in the perioperative period, morbi-mortality was reduced. In children the impact on postoperative outcome of this therapy is not clear.

Objective: To determine the impact of intraoperative goal directed fluid and haemodynamic therapy on postoperative morbi-mortality in children less than 18 years old.

Methods: Systematic review and meta-analysis of randomised and non randomised studies.

RevMan 5.3 sofware was used for statistic analysis.

Results: 23 studies were included with 3389 children among which 21 trials concerned cardiac surgical children and two concerned non cardiac patients:

1° In 3290 children in 21 studies included, mortality was significantly lower in the experimental group (the group with higher above baseline values of regional oxygen saturation, of mixed central venous oxygen saturation, and lower lactate levels) (odds ratio=0.03 [0.01, 0.14], p<0.00001). The quality of evidence (GRADE) was low.

2° In 14 studies with 2347 children included, organ dysfunction was significantly lower in the experimental group

(odds ratio = 0.02 [0.00, 0.08], p <0.00001). The quality of evidence (GRADE) was low.

3° in 8 studies length of hospital stay was significantly lower in the experimental group (p=0.018). The quality of evidence (GRADE) was very low.

Conclusions: Intraoperative goal directed fluid and haemodynamic therapy is not developed in children, there are biomarkers of postoperative adverse outcome in pediatric cardiac surgery.

Research is to be developed in children to clarify the impact of goal directed fluid and hemodynamic therapy on postoperative outcome.

Introduction

Background

In adult surgery, there is evidence that intraoperative Goal Directed Fluid and Haemodynamic Therapy (GDFHT) improves postoperative outcome (mortality, morbidity and length of hospital stay). Several studies have shown that when goal directed fluid and haemodynamic therapy was applied in the perioperative period in high risk patients, mortality, renal and gastro-intestinal complications and infections were reduced [1-7]. In children conclusions concerning this subject are not clear.

Why was it important to do this review?

This review was important to bring some evidence for pediatric intraoperative management using goal directed fluid and haemodynamic therapy to improve postoperative outcome and to develop research in fields where evidence is still unclear and not developed.

How the intervention might work

The aims of the goal directed fluid and haemodynamic therapy are to increase end organ blood flow (oxygen delivery) which results in improved patient outcome. Goal directed fluid therapy and haemodynamic aim to avoid hypovolemia or hypervolemia which can compromise end organ perfusion and oxygen delivery.

Objectives of this study

The main objective was to determine whether intraoperative goal directed fluid and haemodynamic therapy reduced postoperative mortality and or morbidity in children.

Secondary objective was to determine whether intraoperative goal directed fluid therapy diminished postoperative length of hospital stay in children.

Methods

This study was registered in Prospero database as

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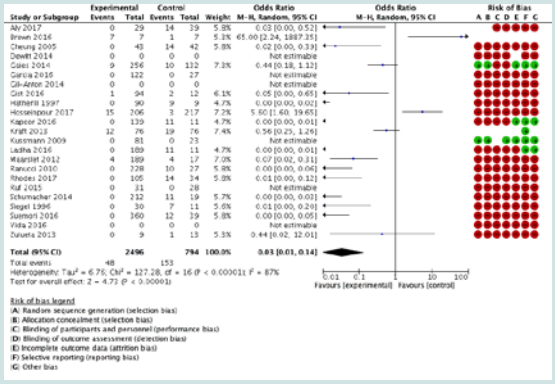

Figure 1: Forest plot of all interventions included and mortality.

[CRD42018103119].

Since this was a systematic review and meta-analysis, ethical approval from the local ethics committee was not necessary.

Inclusion criteria were randomised and non randomised trials where intraoperative goal directed fluid and haemodynamic therapy was applied and compared to standard care in children (patients <18 years old) without any geographic, language or date restrictions.

Intraoperative goal directed fluid and hemodynamic therapy was defined as interventions where fluids (crystalloids and or colloids) and or inotropes and or vasoactive drugs were administered intraoperatively using devices or biomarkers or parameters which measured goals. Goals were defined as: cardiac output, cardiac index, oxygen delivery, oxygen delivery index, oxygen consumption, stroke volume, stroke volume variation, pulse pressure variation, ScVO2(mixed venous oxygen saturation), lactate levels, oxygen extraction ratio, aortic velocity-time integral variation, aortic flow peak velocity, aortic flow peak velocity variation PVI (pleth variation index), NIRS (near infrared spectroscopy).

Precisely, we designed the interventional or experimental group, as the group where the intervention was favorable (for instance higher or normal cardiac index or higher regional oxygen saturation or higher or normal central venous mixed oxygen saturation ScVO2 or lower and normal values of lactate levels or lower vasoactive inotropic scores, lower venous to arterial carbon dioxide difference) or where goal directed fluid and haemodynamic therapy were applied using haemodynamic devices such as PiCCO (pulse contour cardiac output), Vigileo, transoesophageal doppler and echocardiography . The control group was defined as the group where the intervention was not favorable (for instance lower cardiac index or lower values of regional oxygen saturation, lower central venous mixed oxygen saturation ScVO2 or higher lactate levels, higher vasoactive inotropic scores, higher venous to arterial carbon dioxide difference) or where standard care was applied. Standard care was defined as situations where standard parameters were used to monitor haemodynamics such as mean arterial pressure, perfusion pressure, arterial blood pressure, central venous pressure. These interventions were applied intra-operatively (and or in the immediate postoperative period up to 24 h on admission in the PICU (pediatric intensive care unit).

Primary outcome measures were the number of postoperative deaths and number of patients with postoperative complications. Complications were defined as organ failure or dysfunction or infections.

Secondary outcome measures were the number of days spent in hospital

Primary outcomes were postoperative mortality and morbidity until discharge from hospital. Secondary outcome was Length of Hospital Stay (LOS).

Search methods for identification of studies

Titles and abstracts were searched electronically using keywords between 1 October 2018 and 31 January 2019. Once these were found, abstracts with relevant content were analysed and complete articles were searched and screened for further inclusion or exclusion.

We searched for randomised controlled trials and non randomised trials using the following keywords 'fluid therapy OR crystalloids OR colloids OR haemodynamic OR fluid responsiveness OR inotrops in children OR cardiac output OR cardiac index OR oxygen delivery OR oxygen delivery index OR oxygen consumption OR stroke volume OR stroke volume variation OR pulse pressure variation OR mixed venous oxygen saturation OR lactate OR oxygen extraction ratio OR aortic velocity time integral variation OR aortic flow peak velocity variation OR NIRS in children OR outcome in children OR mortality in children OR morbidity in children OR length of hospital stay in children OR randomised trials in children OR non randomised trials in children'.

We used Medline (535009 identified titles), Embase (17536 identified trial titles), Central (37002 identified trial titles), Google Scholar (1540 identified titles), Clinicaltrials.gov (504 identified studies), Abstract Conference (0 titles identified) and DARE (566 identified titles) databases to search for titles, abstracts and complete articles. Other sources like grey literature were also searched.

A flow chart illustrated the search and selection process as recommended by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement [8,9] (Supplemental Figure 1).

Statistic analysis

-Comparisons (interventions) and outcomes (for mortality and morbidity) were collected and analysed with Review Manager

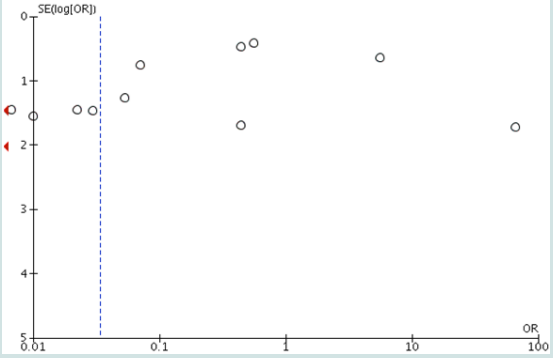

Figure 2: Funnel plot of all interventions included and mortality.

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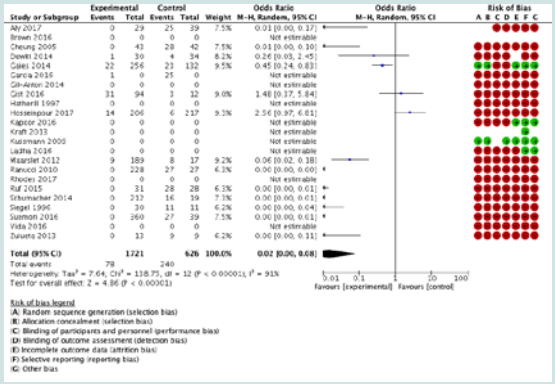

Figure 3: Forest plot of all interventions included and morbidity (Organ dysfunction).

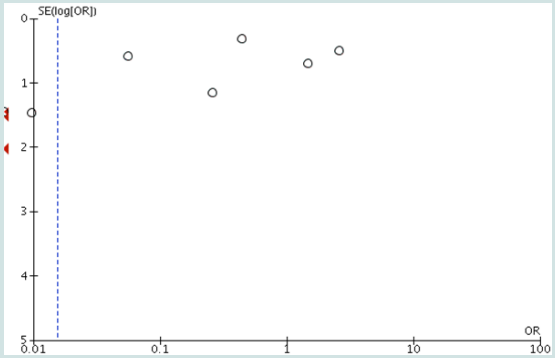

Figure 4: Funnel plot of all interventions included and morbidity (Organ dysfunction).

(RevMan) [Computer program]. Version 5.3.

Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014.

Measures of the treatment effect (intervention effect) were dichotomous for mortality and morbidity (number of deaths, number of patients with complications) and was presented as OR (odds ratio) with a 95% confidence interval ($p<0.05$ was considered significant). Forest plots were used to provide visual summary of the data included.

Forest plots and I^2 statistics were used to assess for heterogeneity in the studies. Funnel plots were used to assess for publication bias.

Sensitivity analysis was done by restricting the analysis to a defined intervention and or to a subgroup of patients with a particular outcome.

-A qualitative description and analysis for LOS was realized since data concerning mean values were not always available in all studies. Median values with Interquartile Ranges [IQR] for LOS were compared between the experimental and the control groups using Wilcoxon test ($p<0.05$ was considered significative) with XLSTAT software 2018.3.

-The unit of analysis issues was the number of deaths for mortality and the number of patients with complications for morbidity in the postoperative period until discharge from hospital and median Length of Hospital Stay (LOS) in the postoperative period in days.

Missing data was not included

The risk of bias in included studies was assessed using the Oxford scale and the tools proposed by the Cochrane Handbook for systematic reviews of interventions included with software [10].

The level of evidence was assessed using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system [11].

Results

33 complete trial articles were retained and analysed for inclusion. 10 studies were excluded because they did not meet the inclusion criteria and 23 were included in the systematic review and meta-analysis. See flowchart in (Supplemental Figure 1).

There were 23 studies included [12-34]. 3 were randomized controlled trials, 12 were prospective observational and 8 retrospective observational trials. Studies found were most of them observational and non interventional, see (Supplemental Tables 1-4) for characteristics.

Effects of interventions

I°) Regional oxygen saturation measured by NIRS: 8 studies in cardiac surgery (3observational retrospective, 4 observational prospective, 1 randomised controlled trial) were included for meta-analysis [12,15-18,27-29].

I.1°) Mortality (Supplemental Figure 2): 7 studies with 910 patients were included for this outcome. Mortality (OR=0.03 [0.01, 0.13], $p<0.00001$) was significantly lower in the experimental group. The I^2 statistics equaled 26 % and thus heterogeneity was very low. All studies had bias (randomisation in the retrospective and prospective trials, blinding and allocation concealment). Analysis with funnel plot (Supplemental Figure 3) showed that the triangle was almost symetrical; the risk of publication bias was present but low and can be explained by the absence of studies which favored the control group or studies without significant results.

Patients with perioperative higher (above baseline values) regional oxygen saturations measured by NIRS in cardiac surgery had

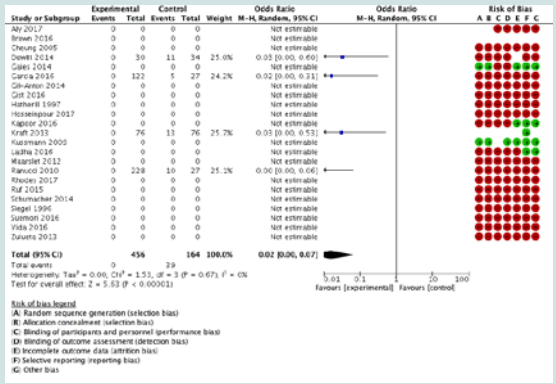

Figure 5: Forest plot of all interventions included and morbidity (Infections).

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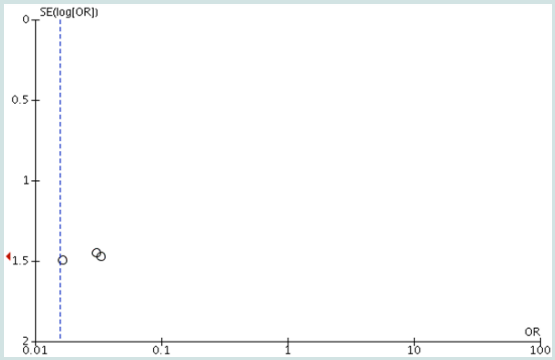

Figure 6: Funnel plot of all interventions included and morbidity (Infections).

a favorable outcome in terms of mortality. The quality of evidence (GRADE) was low (low heterogeneity and presence of bias in all studies).

I.2°) Morbidity (organ dysfunction) (Supplemental Figure 4): 6 studies with 718 patients were included for this outcome. Organ dysfunction (OR=0.02 [0.00, 0.37], p=0.009) was significantly lower in the experimental group. Heterogeneity was high with I^2 statistics equaling 88%. Heterogeneity was due to the different number of patients between the control and experimental groups. The risk of bias in the studies was high (non randomisation, no blinding, No allocation concealment). Analysis with funnel plot (Supplemental Figure 5) showed a truncated triangle, publication bias was present due to the absence of studies favoring the control group or with no significant results. Patients with perioperative higher (above baseline values) regional oxygen saturations measured by NIRS in cardiac surgery had a favorable outcome in terms of organ dysfunction. The quality of evidence GRADE) was low (high heterogeneity and bias in all the studies).

I.3°) Morbidity (infections) (Supplemental Figure 6): one study with 64 patients was included for this outcome (this outcome was not evaluated in the other studies). There were less infections (Necrotizing Enterocolitis) (OR= 0.03 [0.00, 0.60], p=0.02) in the experimental group. Patients with perioperative higher (above baseline values) regional splanchnic oxygen saturations measured by NIRS after cardiac surgery had a favorable outcome in terms of infections (Necrotizing Enterocolitis). The quality of evidence (GRADE) is very low due to the small number of patients and the risk of bias.

I.4°) LOS (Supplemental Table 5) three studies among the eight assessed this outcome [12,15,16].

There was no difference in LOS between the experimental and the control groups when all the three studies were considered together.

The quality of evidence (GRADE) was very low (three studies included and evaluated this outcome among the eight and high risk of bias).

II°) Perioperative lactate levels: 9 studies in cardiac surgery were included for meta-analysis (6 observational prospective and 3 observational retrospective) [19-24,30-32].

II.1°) Mortality (Supplemental Figure 7): 9 trials (6 prospective and 3 retrospective) with 1690 children in cardiac surgery were included for this outcome. Mortality was significantly lower (OR=0.01 [0.00, 0.10], p=0.0003) in children with lower perioperative lactate levels compared to those who had higher lactate levels. All studies had bias (non randomisation, no blinding, no allocation concealment). I^2 statistics (91%) showed high heterogeneity among the studies due to the different number of patients between the experimental and the control groups. Funnel plot (Supplemental Figure 8) showed a truncated triangle, thus publication bias was present due to the absence of trials which favored control groups or with non significant results. In cardiac surgical children with higher perioperative lactate levels mortality was increased. The quality of evidence (GRADE) was low (high heterogeneity and risk of bias).

II.2°) Morbidity (organ dysfunction) (Supplemental Figure 9) 6 studies (3 prospective and 3 retrospective) with 1241 children were included for this outcome. Morbidity (OR= 0.01 [0.00, 0.16], p=0.002) in terms of organ failure was lower in patients with lower perioperative lactate levels. All studies had bias (non randomisation, no blinding, no allocation concealment). I^2 statistics (94%) showed high heterogeneity due to the difference of number of patients between the experimental and the control groups.Funnel plot (Supplemental Figure 10) indicated that publication bias was present due to the absence of trials with favorable outcome for control groups or with non significant results. In cardiac surgical children with higher perioperative lactate levels organ dysfunction was increased. The quality of evidence (GRADE) was low (high heterogeneity and risk of bias).

II.3°) Morbidity (infections) (Supplemental Figure 11): one study with 255 children evaluated this outcome 31. Infections were lower in the experimental group (OR= 0.00 [0.00, 0.06], p=0.0001). The risk of bias was high (non randomised, no blinding, retrospective). The quality of evidence (GRADE) is very low because only one study among 9 was included for this outcome and the risk of bias was high.

II.4°) LOS (Supplemental Table 6): one study evaluated this outcome [21], In this trial, LOS was lower in patients with lower perioperative lactate levels. The quality of evidence (GRADE) was very low (one study among 9 and high risk bias).

III°) Perioperative Lactate levels and $ScVO_2$:

Three studies were included for meta-analysis (one prospective and two retrospective).

III.1°) Mortality (Supplemental Figure 12): three studies with 828 children in cardiac surgery evaluated this outcome using lactate levels and ScVO2. In one study mortality was higher in the experimental group and in the two other studies mortality was higher in the control groups [23,31,32]. Taking the three studies together there was no difference between the experimental and the control groups in terms of mortality (OR=0.02 [0.00, 17.18], p=0.25).

All studies had bias (no randomisation, no blinding, no allocation concealment). I^2 statistics (95%) showed high heterogeneity due to the difference between the number of patients in the experimental and the control groups. Funnel plot (Supplemental Figure 13) showed that publication bias was present due to the absence of trials favoring experimental and control groups or studies with non significant results. The quality of evidence (GRADE) was low due to the high

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risk of bias and heterogeneity.

III.2°) Morbidity (organ dysfunction) (Supplemental Figure 14): Two studies with 678 Children evaluated this outcome [31,32]. There was no difference in terms of organ dysfunction between the experimental and the control group (OR= 0.01 [0.00, 4534.49], p=0.5). All the two studies had bias (non randomisation, no blinding, no allocation concealment). I^2 statistics (98%) showed high heterogeneity due to the difference of number of patients between the experimental and the control groups.

Funnel plot (Supplemental Figure 15) showed that publication bias was high due to the absence of trials favoring both experimental and control groups or with non significant results. The quality of evidence (GRADE) was low due to high risk of bias and high heterogeneity.

III.3°) Morbidity (infections) (Supplemental Figure 16): one study evaluated with 255 patients this outcome [31]. Infections were lower in the experimental group (OR=0.00 [0.00, 0.06], p=0001). The risk of bias was high (non randomised, no blinding, retrospective). The quality of evidence (GRADE) was very low because only one study among the three evaluated this outcome and bias was high.

III.4°) LOS was not evaluated.

IV°) ScVO2 (with Vigileo) + lactate levels: Two studies one prospective and one retrospective with 405 children in cardiac surgery were included [23,31].

IV.1°) Mortality (Supplemental Figure 17): Mortality was lower in the experimental group (OR=0.00 [0.00, 0.02], p<0.0001). The two studies had bias (non randomised, not blinded, no allocation concealment) [23,31]. I^2 (42%) statistics showed that heterogeneity was low. Funnel plot (Supplemental Figure 18) showed that publication bias was very high due to the absence of studies which favored experimental and control groups or with non significant results. The quality of evidence (GRADE) was low (high bias).

IV.2°) Morbidity (organ dysfunction) (Supplemental Figure 19) one study evaluated this outcome [31]. Organ dysfunction was lower in the experimental group (OR=0.00 [0.00, 0.00], p<0.00001). Quality of evidence (GRADE) was low (only one study over two evaluated this outcome).

IV.3°) Morbidity (infections) (Supplemental Figure 20): one study evaluated this outcome [31].

Infections were lower in the experimental group (OR=0.00 [0.00, 0.06], p=0.0001). The quality of (GRADE) evidence was very low (only one study over two evaluated this outcome and high bias).

IV.4°) LOS: not evaluated

V°) PiCCO system

Two studies were identified and included a prospective trial in cardiac surgery and a randomized controlled trial in severely burned children [13,25].

V.1°) Mortality (Supplemental Figure 21): one study in 152 children with severe burns evaluated this outcome [13]. There was no difference in terms of mortality (OR= 0.56 [0.25, 1.26], p=0.16) between the experimental and the control groups. The risk of bias was unclear: randomisation and the blinding were not clear. The quality of evidence (GRADE) was very low because only one study was included.

V.2°) Morbidity (organ dysfunction): this outcome was not evaluated.

V.3°) Morbidity (infections) (Supplemental Figure 22): one study evaluated this outcome in 152 severely burned children [13]. There was no difference in terms of infections (OR=0.49 [0.18, 1.31] between the experimental and the contral groups. The risk of bias was unclear: randomisation and blinding were not clear. The quality of evidence (GRADE) is very low because only one study was included.

V.4°) LOS (Supplemental Table 7): the two studies evaluated this outcome. LOS was not different between the two groups (p= 0.317). The risk of bias was high (no randomisation, no blinding). The quality of evidence (GRADE) is very low (only two studies included high risk of bias).

VI°) Maximum vasoactive inotrop score (VIS)

VI.1°) Mortality (Supplemental Figure 23): two studies with 537 children in a prospective cardiac surgery trial and in a retrospective study were included [26,33].

Mortality (OR= 0.44 [0.18, 1.12], p=0.09) was not different between the experimental and the control groups. The risk of bias was high in the two studies (non randomisation, no blinding). The quality of evidence (GRADE) was very low (only two studies found and high risk of bias).

VI.2°) Morbidity (organ dysfunction) (Supplemental Figure 24): The two studies were included. Morbidity (OR= 0.02 [0.00, 15.26], p=0.25) in terms of organ failure was not different between the experimental and the control groups. The risk of bias was high in the two studies (non randomisation, no blinding). The I^2 (96%) statistics showed high heterogeneity due to the difference of the number of patients between the experimental and the control groups. The quality of evidence (GRADE) was very low.

VI.3°) Morbidity (infections) (Supplemental Figure 25), one study was included [33]. Morbidity in terms of infections (OR=0.02 [0.00, 0.31], p=0.006) was lower in the experimental group. The risk of bias was high (no randomisation, no blinding). The quality of evidence (GRADE) was very low.

VI.4°) LOS (Supplemental Table 8) was evaluated in one study and was low in the experimental group [33]. The risk of bias was high (no randomisation, no blinding). The quality of evidence (GRADE) is very low.

VII) Venous to arterial carbon dioxide difference

One retrospective study with139 cardiac surgical patients admitted to PICU was included [34].

VII.1°) Mortality (Supplemental Figure 26): Mortality (OR= 0.01 [0.00, 0.12], p=0.0006) was lower in the experimental group. The risk of bias was high (no randomisation, no blinding). The quality of evidence (GRADE) was very low.

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VII.2°) Morbidity (organ dysfunction) (Supplemental Figures 27- 29) organ failure (acute kidney failure p=0.005, ECMO p=0.004, CPR p=0001) was significantly low in the experimental group. The risk of bias was high (no randomisation, no blinding). The quality of evidence (GRADE) very is low.

VII.3°) Morbidity (infections): was not evaluated.

VII.4°) LOS (Supplemental Table 9) was lower in the experimental group. The quality of evidence was very low.

VIII) Transoesophageal doppler probe

One randomised controlled trial with 14 children in scoliosis surgery was found [14].

VIII.1°) Mortality: was not evaluated.

VIII.2°) Morbidity (organ dysfunction) (Supplemental Figure 30): Organ dysfunction (OR=65.00 [2.24, 1887.35], p=0.02) (in terms of acute kidney failure and alterations of motor evoked potentials) was higher in the experimental group. The risk of bias was unclear (in terms of randomisation, in terms of allocation concealment and in terms of blinding), there was no compliance to the protocol. The number of patients was too low. The quality of evidence (GRADE) was very low.

VIII.3°) Mortality (infections): not evaluated.

VIII.4°) LOS: not evaluated.

IX.1°) all interventions included

23 studies were identified with 3389 children. 3 studies were randomised controlled. 12 prospective observational and 8 were retrospective observational. 21 studies concerned 3223 cardiac surgical children with congenital heart disease. Only two studies with 166 children concerned noncardiac patients: one study concerned PiCCO in 152 children with severe burns and one concerned transoesophageal doppler in 14 children in scoliosis surgery.

IX.1°) Mortality (Figure 1): 21 studies were included among the 23 identified with 3290 children. Mortality was significantly lower in the experimental group (OR=0.03 [0.01, 0.14], p<0.00001). I^2 statistics (87%) showed high heterogeneity among the studies due to the different number of patients in the experimental and control groups. The risk of bias was high in all the studies (in terms of randomisation, allocation concealment and blinding). Funnel plot (Figure 2) showed an almost truncated triangle, suggesting that publication bias was present due to the absence of trials which favored the control groups or with non significant results. The quality of evidence (GRADE) was low (high heterogeneity and bias)

IX.2°) Morbidity (organ dysfunction) (Figure 3): 14 studies among the 23 trials with 2347 children were included for this outcome. Organ dysfunction was lower in the experimental group (OR=0.02 [0.00, 0.08], p<0.00001). I^2 statistics (91%) showed high heterogeneity due to the difference in the number of patients between the experimental and the control groups. The risk of bias was high in all the studies (in terms of randomisation, allocation concealment and blinding). Funnel plot (Figure 4) showed a truncated triangle suggesting that publication bias was due to the absence of trials which favored the control groups or with non significant results. The quality of evidence (GRADE) was low (high heterogeneity and bias).

IX.3°) Morbidity (infections) (Figure 5): 4 studies among the 23 with 620 children were included for this outcome. Morbidity in terms of infections was lower in the experimental group (OR= 0.02 [0.00, 0.07], p<0.00001. I^2 statistics (0%) showed that there was no heterogeneity among the studies. Bias was present in all studies in terms of randomisation, allocation concealment and blinding. Funnel plot (Figure 6) showed a truncated triangle suggesting the presence of publication bias due the absence of studies which favored control or with non significant results. The quality of evidence was low (high risk of bias) to moderate (no heterogeneity).

IX.4°) LOS (Supplemental Table 10): 8 studies evaluated this outcome. LOS was significantly lower in the experimental group. Bias was present in all studies (randomisation, allocation concealment and blinding). The quality of evidence (GRADE) was very low (only 8 studies among 23 evaluated this outcome).

No trial was found concerning pulmonary artery catheter in children and outcome.

One study concerning intraoperative transoesophageal echocardiography was found but not included in the meta-analysis because adults and children were included and thus did not meet the inclusion criteria [35]. However this study found that LOS was reduced in patients when a second intraoperative transoesophageal echocardiography was performed.

Discussion

Overall completeness, applicability and quality of evidence

This meta-analysis concerned children (under 18 years of age) in the perioperative period (intraoperative up to the immediate postoperative period i.e. first 24 hours postoperatively). The majority of patients (more than 90%) were cardiac surgical patients (3223 children among 3389 patients). Only 166 children were non cardiac patients (152 with severe burns and 14 in scoliosis surgery). Several parameters were used to monitor haemodynamics intraoperatively and or postoperatively in these patients : cerebral, renal, splanchnic, somatic oxygen saturation; lactate levels and lactate clairance, mixed central venous oxygen saturation via blood samples or using Vigileo, cardiac output using PiCCO system and transoesophageal doppler, venous to arterial carbon dioxide difference. Most of the studies were retrospective and prospective observational (comparing outcome between experimental groups where these parameters had optimal values and control groups where these parameters were suboptimal). Only three were interventional and applied stricto sensu goal directed therapy protocols compared to standard care [13,14,32]. Kraft et al. found no difference between the two groups;

Hosseinpour et al. and Brown et al. found that outcome was adverse in the experimental group but the quality of evidence was very low due to the presence of bias in all the three studies and the small number of patients.

Nevertheless, this systematic review and meta-analysis evidenced that primary outcome (mortality and morbidity) was lower in cardiac surgical children who had optimal haemodynamic parameter values with overall low quality of evidence according to GRADE classification

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because of high risk bias and high heterogeneity. Secondary outcome

(Length of hospital stay, LOS) was also lower in the experimental group but overall quality of evidence was very low because not all the studies assessed this outcome and bias was present in all the studies.

In cardiac surgical children when haemodynamics were monitored using the above mentioned variables or parameters (regional oxygen saturation, mixed central venous oxygen saturation, lactate levels, cardiac output, venous to arterial carbon dioxide difference) adverse outcome was significantly higher in patients with suboptimal variable values. Randomised controlled trials (RCT) where goal directed fluid and haemodynamic therapy (GDFHT) using these parameters or biomarkers should be developed to clarify the impact of this therapy on postoperative outcome in cardiac pediatric patients since well conducted prospective studies without bias concerning GDFHT in this population are lacking. Trials using echocardiography to assess postoperative outcome in cardiac or non cardiac pediatric patients are lacking despite studies validating this device for fluid reponsiveness in children under general anesthesia [36,37]. There was one retrospective study which evaluated transoesophageal echocardiography during congenital heart disease surgery and postoperative outcome but this trial included adults and children and found LOS to be lower in the group where there was a second intraoperative transoesophageal echocardiograpy [35]. Concerning transoesophageal doppler, several studies in non cardiac surgical children under general, caudal and epidural anaesthesia have assessed cardiac output using this device [38-40]. Studies concerning postoperative outcome with this device in children are lacking ; the only study found was a trial in 14 scoliosis surgery children where outcome was adverse in the transoesophageal group but this study was stopped earlier because of non compliance to the protocol and thus clinical evidence was very low for this trial [14]; further studies should be conducted with the transoesophageal doppler in children to clarify its impact on postoperative outcome ; in adults it has been used in goal directed fluid and haemodynamic therapy and has proven to reduce postoperative morbidity [41].

One study compared PiCCO and transoesophageal doppler in PICU children and found that in non cardiac surgical patients the two devices showed equivalent haemodynamic variables but this observation was not evidenced in cardiac pediatric patients [42]. Two studies evaluated PiCCO and outcome [13,25]; Kraft et al found that mortality and morbidity was not different between the two groups ; Gil-Anton et al found LOS to be lower in the experimental group ; the quality of evidence was very low. More studies with less bias should be developed with PiCCO in children intraoperatively to clarify its impact on postoperative outcome.

Vigileo was used to monitor ScVO2 in two trials where mortality was lower in patients with higher ScVO2 values, the quality of evidence was low; organ failure and infections were lower in children intraoperatively with higher ScVO2 values, the quality of evidence was low [23,31]. More studies with less bias need to be developed with vigileo in children to clarify its impact on postoperative outcome.

Limits

Potential biases in the review process: Many studies had results favoring the experimental groups. Studies which favored the control groups or with non significant results were lacking. Studies with negative or positive results remain most of the time unpublished [43]. It is also important to publish these studies to reduce the publication bias.

Risk of bias in included studies: Allocation (selection bias) : was not precised in most of the studies

Blinding (performance bias and detection bias) : there was no blinding in most of the studies.

Incomplete outcome data (attrition bias): almost all of the studies except two studies did not precise the presence or the absence of incomplete data [18,26].

Selective reporting (reporting bias): presenting exclusively studies with favorable results could be a source of bias.

Other potential sources of bias: the different number of patients in the experimental and control groups could be a source of bias.

Heterogeneity among the studies

Strength of this study: 1) This trial clarified that intraoperative goal directed fluid and hemodynamic therapy is not developed in children. Future research will be conducted in developing trials with less bias to assess its impact on outcome.

2) Several parameters of adverse outcome in cardiac surgery have been identified and should be integrated in goal directed fluid and hemodynamic therapy research protocols with less bias to determine their impact on outcome.

Conclusions and Recommendation

1°) Goal directed fluid and haemodynamic therapy in the pediatric surgical population is not developed.

2°) In cardiac surgical patients intraoperative and postoperative suboptimal values of regional oxygen saturation, mixed central venous oxygen saturation, lactate levels, and venous to arterial carbon dioxide difference are predictive of postoperative adverse outcome. RCT where GDFHT using these parameters need to be developed to clarify the impact of this practice on postoperative outcome in children.

3°) In non cardiac surgical pediatric patients, research should be directed in developing randomised controlled trials or prospective trials with less biases to clarify the impact of intraoperative monitoring with echocardiography, transoesophageal doppler, PiCCO, Vigileo to guide fluid and haemodynamic therapy on postoperative outcome in major surgery.

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