Reducing Mortality in the Perioperative Period: A Continuous Update

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18.1 Introduction

According to the EUSOS study, perioperative mortality for noncardiac surgery is 1–4 % [1], considering that up to 230 million surgical procedures are performed each year in the world [2], even a small reduction would have a tremendous impact on public health.

The first Consensus Conference on mortality reduction in the perioperative period was published in 2012 [3]. Three years later an official update was held. Thirteen interventions showing a significant impact on mortality were selected and are the object of this book [4]. Three topics included in the first Consensus Conference were excluded (clonidine, perioperative supplemental oxygen, and chlorhexidine oral rinse), and two new interventions were added (tranexamic acid and remote ischemic preconditioning).

This chapter briefly reports the papers published after the second Consensus Conference was held, which showed a statistical significant effect on perioperative mortality (Table 18.1).

18.2 Methods

A sensitive PubMed search was performed to systematically identify all papers dealing with interventions influencing perioperative mortality, published since the Consensus Conference Update. The same three search strategies were used (Table 18.1); time limits were set from the 7th of March 2015 and the 30th of January 2016. Further topics were identified by cross-checking of references.

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Box 18.1 The full three search strategies used to identify all RCT and the meta-analysis of RCT reporting a significant effect on perioperative mortality

Systematic[sb] AND (surgery[tiab] OR surgic*[tiab] OR operation*[tiab]) AND ((myocardial AND infarction) OR (death* OR survival OR mortality OR prognosis)) AND (prevent* OR reducti* OR reduci*)
(Surgery[tiab] OR surgic*[tiab] OR operation*[tiab]) AND ((death* OR survival OR mortality)) AND (prevent* OR reducti* OR reduci*) AND (significat* OR significan*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt]))
(Dead[tiab] or death[tiab] or die[tiab] or died[tiab] or mortality[tiab] or fatalit*[tiab] or exitus[tiab] or surviv*[tiab]) and (“anesthesia”[tiab] OR “cardiac arrest”[tiab] or “critical care”[tiab] or sepsis[tiab] or “critical illness”[tiab] or “critically ill” [tiab] or “ARDS”[TIAB] or “acute respiratory distress syndrome”[tiab] OR “ecmo”[tiab] OR “intensive care”[tiab] or emergen*[tiab]) AND (“randomized controlled trial”[tiab] OR “controlled clinical trial”[tiab] OR “randomized controlled trials”[tiab] OR blind*[tiab] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR placebo*[tiab] OR random*[tiab]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt] OR pediatrics[mh])

Selected papers fulfilled all the following criteria: (a) published in a peer-reviewed journal, (b) dealing with a nonsurgical intervention (drug/technique/strategy) in adult patients undergoing any surgery, and (c) reporting a statistically significant reduction or increase in mortality, (d) conduced as randomized trial (RCT) or meta-analysis of RCT.

18.3 Interventions That Have Shown an Effect on Perioperative Mortality

The three search strings described in Box 18.1 identified 362, 355, and 1,092 results, respectively. After a careful screening, nine studies [5–13], dealing with seven different interventions, were included in the present update. The summary of new evidences at the end of this chapter reports the main characteristics of the selected papers.

Three interventions not already selected by the Consensus Conference have been found to possibly improve survival: miniaturized extracorporeal circulation (MECC) [5], non-adrenergic vasopressors [6], and perioperative goal-directed hemodynamic therapy (GDHT) [7]. The other six papers dealt with four interventions already present in the Consensus Conference Update: volatile agents [8], perioperative intra-aortic balloon pump (IABP) [9, 10], levosimendan [11, 12], and remote ischemic preconditioning (RIPC) [13].

Eight out of nine studies were set in cardiac surgery [5, 6, 8–13]. Two papers focused on a mixed population (i.e., surgical and medical) [6, 13]. All the selected papers were meta-analyses of RCTs; one of them included also observational studies which were analyzed separately [10], and two were network meta-analyses [5, 8]. All selected papers dealt with intervention that showed a positive effect on survival.

18.4 Miniaturized Extracorporeal Circulation in Coronary Artery Bypass Grafting

Coronary artery bypass grafting is associated with a reduction of mortality in extensive coronary artery disease. The gold standard technique is the CABG with the use of cardiopulmonary bypass (CPB). Nevertheless conventional extracorporeal circulation (CECC) is believed to be a major determinant for postoperative morbidity. Consequently novel solutions have been developed to reduce its impact, such as off-pump CABG (OPCAB) and MECC. Miniaturized extracorporeal circulation reduces the air-blood contact using a shorter circuit and no venous reservoir: therefore, it lowers blood loss and need for transfusions and minimizes inflammatory response.

Kowalewski et al. [5] conducted a network meta-analysis comparing the effect of these three strategies on mortality and postoperative complications. They selected 134 RCTs, enrolling 22,778 patients. Data on mortality were extracted from 50 RCTs (17,638 patients). MECC and OPCAB were associated with a significant reduction of all-cause mortality (OR (95 % CI), 0.46 (0.22–0.91), and 0.75 (0.51–0.99)) when compared with CECC. These techniques offered a significantly higher protection against cerebral stroke, postoperative atrial fibrillation, and renal dysfunction, while no significant differences among three strategies were seen in regard to myocardial infarction. No significant difference between OPCAB and MECC was observed from direct comparison, but the hierarchy of numerical treatments emerging from the probability inference analyses was MECC >OPCAB >CECC.

Previous observational studies and meta-analyses reported increased long-term mortality with OPCAB. Selection bias seems to be the obvious explanation for the discrepancies between observational and randomized strata. Patients included in the OPCAB group were more likely to be at higher baseline risk.

The main limitations of this work are that the authors did not have access to individual patients' data and that the number of event observed was small.

18.5 Non-adrenergic Vasopressors in Vasodilatory Shock

Non-adrenergic vasopressors are a group of drugs that are used in hemodynamic shock in association with or instead of catecholamines. Their use reduces catecholamines side effects, such as increased myocardial oxygen consumption and arrhythmias. Moreover, they are essential in the treatment of late-phase shock, when standard treatment became ineffective.

Belletti et al. conducted an extensive meta-analysis, including twenty RCTS (1,608 patients), to investigate the effect on mortality of non-adrenergic vasopressor in vasodilatory shock [6]. The intervention agents were vasopressin, terlipressin, and methylene blue. The comparators were placebo, standard treatment, norepinephrine, and dopamine. Most of the selected studies were performed in the setting of sepsis (10/20) and in the setting of cardiac surgery (7/20). Overall pooled analysis showed that the use of non-adrenergic vasopressors was associated with a significant mortality reduction (RR (95 % CI): 0.88 (0.79–0.98), $p=0.02$). Considering the study drugs independently, all agents were associated with a nonsignificant trend toward improved survival of the same direction and magnitude. When analyzing different settings, non-adrenergic vasopressors were found to reduce mortality both in sepsis (RR (95 % CI): 0.87 (0.77–0.98), $p=0.02$) and cardiac surgery (RR (95 % CI): 0.16 (0.04–0.69), $p=0.01$). The authors speculate that the survival benefit observed might be a consequence of their catecholamine-sparing effect, rather than a beneficial effect per se.

18.6 Perioperative Goal-Directed Hemodynamic Therapy in Noncardiac Surgery

Goal-directed hemodynamic therapy (GDHT) is the use of a hemodynamic optimization algorithm that aims to achieve normal or supranormal hemodynamic values, through fluids, vasopressors, and inotropes. This implies the use of more or less invasive hemodynamic monitoring. The objective is to prevent hypoperfusion and imbalance between oxygen delivery and consumption.

Ripollés-Melchor and colleagues [7] conducted a meta-analysis of RCTs to assess whether this approach reduces complications and mortality compared to conventional fluid therapy in noncardiac surgery patients. Studies where GDHT was limited to the intraoperative period were excluded. Twelve RCTs and 1,527 patients were included. Mortality was analyzed in all RCTs included and was significantly reduced by perioperative GDHT (RR (95 % CI): 0.63 (0.42–0.94), $p=0.02$). In subgroup analyses, mortality was reduced only when a supranormal target was set (RR (95 % CI): 0.42 (0.23–0.76), $p=0.004$) and when perioperative GDHT was performed (RR (95 % CI): 0.61 (0.39–0.96), $p=0.03$). No significant difference in the complication rate was detected. In sensitivity analysis, authors found that if studies with lower methodological quality were excluded, there were no differences between GDHT and standard fluid therapy.

18.7 Volatile Agents in Cardiac Surgery

Volatile agents are among the few interventions that might reduce perioperative mortality [3, 4], probably through their ability to mimic the early phase of ischemic preconditioning.

Here we sum the results of the only meta-analysis published since the Consensus Conference Update, while details on this intervention are discussed in a dedicated chapter (Chap. 4).

Zangrillo et al. [8] performed a Bayesian network meta-analysis to assess whether the cardioprotective properties of volatile agents and of RIPC have survival effects in patients undergoing cardiac surgery. To be included, the studies had to compare TIVA to a combined plan including the administration of a volatile agent and/or to include the comparison between the use of RIPC and not. A total of 55 RCTs were selected, randomizing 6,921 patients, of whom 39 % (in 50 studies) received volatile agents, 37 % (in 41 studies) received TIVA, 13 % (in 7 studies) received RIPC+TIVA, and 11 % (in 15 studies) received RIPC+volatile agents. The most common pairwise comparison was volatile agents versus TIVA, present in 34 (62 %) of the selected studies. Through simple direct comparison, volatile agents significantly reduced mortality when compared to TIVA (OR (95 % CI): 0.56 (0.36–0.88), $p = 0.01$). This advantage was maintained when the Bayesian hierarchical model was used (OR (95 % CI): 0.50 (0.28–0.91)). As discussed later on this chapter, the Bayesian network meta-analysis assessed an additive positive effect of volatile agents and RIPC when compared to TIVA with or without RIPC.

18.8 Preoperative Intra-aortic Balloon Pump in Cardiac Surgery

Cardiac surgery may lead to a variable degree of myocardial stunning and depressed contractility, which can cause postoperative low cardiac output syndrome (LCOS). Intra-aortic balloon pump (IABP), which enhances myocardial perfusion and lowers left ventricle work, has been used to prevent this phenomenon in hemodynamic stable patients at high risk of perioperative complications.

The impact of preoperative IABP on mortality has already been stated in the Consensus Conferences by Landoni et al. [3, 4], and details about this intervention have already been described in Chap. 10. This paragraph deals with the two significant meta-analyses published since the Consensus Conference update.

Pilarczyk et al. [9] analyzed nine RCTs that compared aortic counterpulsation started preoperatively with no intervention in 1,171 adult patients undergoing cardiac surgery. The use of preoperative IABP seemed to reduce hospital mortality (OR (95 % CI): 0.38 (0.23–0.68), $p < 0.001$); this effect was maintained when comparing only on-pump CABG studies (OR (95 % CI): 0.27 (0.13–0.55), $p < 0.001$). In addition, a significant reduction in LCOS and length of ICU stay was noted. Complications were reported in seven out of nine studies, with overall incidence being 5.6 %. Most frequent complications were limb ischemia and hematoma.

Poirier's meta-analysis [10] included both RCTs and observational studies, which were analyzed separately. A total of 11 RCTs and 22 observational studies were included. In this meta-analysis, the interventional group received preoperative IABP, while control group did not. The analysis of RCT confirmed a reduction in in-hospital mortality (OR (95 % CI): 0.2 (0.09–0.44), $p < 0.001$), 30-day mortality (OR (95 % CI): 0.43 (0.25–0.76), $p = 0.003$), length of ICU stay (−1.47 day, 95 % CI: – 1.82–1.12, $p < 0.001$), and length of hospital stay (−3.25, 95 % CI: −5.18–1.33, $p < 0.001$). However, such benefit could not be confirmed in data obtained from observational studies, despite inclusion of much larger number of patients with higher baseline risk profiles. Furthermore, severe IABP-related complications were reported in 3 % of patients.

The RCTs included in both meta-analyses overlapped and showed important limitations. First, five RCTs have been performed by the same group, second some RCTs were funded by the industry, third sample size was small, and fourth the rate of IABP crossover varied widely.

18.9 Levosimendan in Cardiac Surgery

Levosimendan is a calcium sensitizer with inotropic and vasodilatory effects that has been found to improve cardiac output in patients with low-output heart failure without increasing cardiac work. The Consensus Conference identified this drug as potentially lifesaving in the perioperative period [3, 4], and details about available evidences and use are described in this book in a dedicated chapter (Chap. 7).

Since the Consensus Conference update, two novel meta-analyses have been published, showing a significant effect on mortality.

Qiao and colleagues [11] assessed the effect of levosimendan on mortality of high-risk (i.e., patients who developed multiple organ dysfunction syndrome) cardiac surgical patients. Ten RCTs (440 patients) were included in the final analysis. In four trials, control group received placebo, while in six control group received an alternative inotropic agent, either dobutamine or milrinone. The use of levosimendan was associated with a significant reduction in perioperative mortality (OR (95 % CI): 0.35 (0.18–0.71), $p = 0.003$), atrial fibrillation (OR (95 % CI): 0.48 (0.29–0.78), $p = 0.003$), myocardial infarction (OR (95 % CI): 0.26 (0.07–0.97), $p = 0.04$), and acute renal failure (OR (95 % CI): 0.26 (0.12–0.60), $p = 0.002$). The subgroup analyses showed that the survival benefit of levosimendan was maintained when compared to each inotropic agent; unfortunately the effect compared with placebo was not reported.

Zhou and collaborators [12] focused their attention on the beneficial effects of levosimendan on renal function after cardiac surgery. They selected 13 RCTs concerning 1,254 adult cardiac surgery patients. Postoperative incidence of acute kidney injury was significantly reduced by levosimendan (OR (95 % CI): 0.51 (0.34–0.76), $p = 0.001$). Accordingly a lower rate of renal replacement therapy was observed in the intervention group (OR (95 % CI): 0.43 (0.25–0.76), $p = 0.002$). Again, a survival benefit for patients treated with levosimendan was documented (OR (95 % CI): 0.41 (0.27–0.62), $p = 0.001$).

The sample size of the RCTs included in these meta-analyses was small. Moreover, data on long-term mortality were still inconclusive.

18.10 Remote Ischemic Preconditioning in Cardiac Surgery

Ischemic preconditioning is a response at cellular level to brief sublethal episodes of ischemia leading to a major protection against subsequent lethal ischemia. Remote ischemic preconditioning consists in the stimulation of short episodes of ischemia and reperfusion in a tissue different from the heart, inducing myocardial protection from ischemia. This conservative and cost-effective technique has been selected by the Consensus Conference update [4], and it is described in detail in Chap. 15.

Since then, two meta-analyses dealing with RIPC have been published.

Le Page and colleagues [13] conducted an extensive research on the effects of RIPC in mixed population, including both cardiac surgery and interventional cardiology patients. The primary end point was myocardial injury, while all-cause mortality was a secondary end point. Forty-four RCTs, involving 5,317 patients, were selected. Among them 22 RCTS were conducted in cardiac surgery (3,093 patients). The authors demonstrated a significant reduction of the myocardial injury markers (troponin area under the curve, OR (95 % CI): −0.27 (−0.36 to –0.18), $p<0.001$), and significance was maintained in the subgroup analysis involving only adult cardiac surgery patients. All-cause mortality occurring over a year after the initial event was significantly reduced by RIPC in three studies (OR (95 % CI): 0.27 (0.13, 0.58), $p=0.0008$). Nonsignificant reduction was observed in short-term all-cause mortality (30 days and less than a year) (OR (95 % CI): 0.79 (0.49, 1.27), $p=0.33$).

In the Bayesian network meta-analysis by Zangrillo et al. already mentioned above [8], the effect on mortality of RIPC in association with either volatile agents or TIVA was studied through simple direct comparison and Bayesian hierarchical model. Direct comparison did not show any significant difference in mortality associated with RIPC, regardless of the anesthetic regimen. Instead, the Bayesian analysis showed a survival benefit associated with the combination of RIPC and volatile agents when compared to both TIVA (OR (95 % CI): 0.15 (0.04–0.55)) and TIVA+RIPC (OR (95 % CI): 0.19 (0.04–0.94)). According to the authors, the probability that the association of volatile agents and RIPC is the best conduct in cardiac surgery is 0.96.

The authors identified several limitations to their work. First, included RCTs were small, single center, and not double blind. Second, in some studies, confounding factors were not disclosed, e.g., the use of sulfonylurea, theophylline, and allopurinol, which can interfere with the preconditioning mechanism, and the total amount of intraoperative opioids that can influence volatile cardioprotective effects.

Conclusion

Evidence-based medicine is constantly evolving. In 11 months, nine papers, dealing with seven interventions, with a significant effect on perioperative mortality were published. Three new interventions have been found to possibly improve survival, MECC, non-adrenergic vasopressors, and GDHT. The other six papers dealt with four interventions already selected in the Consensus Conference Update: volatile agents, perioperative IABP, levosimendan, and RIPC. Goal-directed hemodynamic therapy was the only intervention set in noncardiac surgery. All the selected papers were meta-analyses of RCTs. All selected papers dealt with intervention that showed a positive effect on survival.

18.11 Summary of the New Evidences

New topic	Intervention	Author	Control	Setting	*N* of RCT	*N* of patients	Size effect	Notes
Yes	Miniaturized extracorporeal circulation	Kowalewski M	Conventional extracorporeal circulation	CABG	134	22,778	OR 0.46 (95 % CI 0.22–0.91)	Network meta- analysis, comparing also off-pump CABG
	Vasopressin, terlipressin or methylene blue	Belletti A	Placebo or norepinephrine or dopamine or standard treatment	Vasodilatatory shock (cardiac surgery/ critically ill (sepsis))	20	1,608	RR 0.88 (95 % CI 0.79–0.98)	Multiple comparators Mixed population
	Perioperative goal-directed hemodynamic therapy	Ripollés-Melchor J	Conventional fluid therapy	Noncardiac surgery	10	1,527	RR 0.63 (95 % CI 0.42–0.94)	

No	Volatile agents	Zangrillo A	TIVA	CCH	55	6,921	OR 0.56 (95 % CI 0.36–0.88)	Network meta-analysis (volatile, TIVA ± RIPC). Significant effect in direct comparison for volatile vs TIVA (36 studies, 3,680 patients)
	Preoperative IABP	Poirier Y	No intervention	CCH	11	1,293	OR 0.20 (95 % CI 0.09–0.44)	Observational studies were included, but were analyzed separately
		Pilarczyk K	No intervention	CCH	9	1,171	OR 0.38 (95 % CI 0.23–0.63)	
	Levosimendan	Zhou C	Placebo or dobutamine or milrinone	CCH	13	1,254	OR 0.43 (95 % CI 0.25–0.76)	Multiple comparators
		Qiao L	Placebo or dobutamine or milrinone	CABG(high-risk surgical patients)	10	440	OR 0.35 (95 % CI 0.18–0.71)	Multiple comparators
	Remote ischemic preconditioning	Le Page S	No intervention	CCH and interventional cardiology	44	5,317	OR 0.27 (95 % CI 0.13–0.58)	Mixed population. Long -term mortality was reported only in three RCTs (383 patients)

95 % CI 95 % confidence interval, *CABG* coronary artery bypass graft, *CCH* cardiac surgery, *IABP* intra-aortic balloon pump, *N* number, *OR* odd ratio, *RCT* randomized controlled trial, *RIPC* remote ischemic preconditioning, *RR* relative risk, *TIVA* total intravenous anesthesia

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