A Bayesian network meta-analysis on the effect of anesthetic drugs in cardiac surgery.

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Abstract

We carried out both a pair-wise and a Bayesian network meta-analysis, on 38 randomised trials, to assess how volatile-based anaesthesia (desflurane, isoflurane or sevoflurane) and total intravenous anaesthesia (TIVA) influence patients' survival after cardiac surgery. A network meta-analysis allow to compare different treatments that were never properly compared. On the basis of statistical inference, it is possible to establish which treatment is superior reaching, through indirect comparison, reliable conclusions otherwise difficult to achieve. The standard meta-analysis showed that the use of a volatile agent was associated with a reduction in mortality when compared to TIVA at the longest follow-up available (25/1994 [1.3%] in the volatile group versus 43/1648 [2.6%] in the TIVA group, odds ratio=0.51, 95% confidence interval 0.33-0.81, p for effect=0.004). The Bayesian network meta-analysis showed that sevoflurane (posterior mean of odds ratio =0.31, 95% credible interval 0.14-0.64) and desflurane (posterior mean of odds ratio =0.43, 95% credible interval 0.21-0.82) were individually associated with a reduction in mortality when compared to TIVA. Anaesthesia with volatile agents appears to reduce mortality after cardiac surgery when compared to TIVA, especially when sevoflurane or desflurane are used.

Introduction

Volatile agents have documented pharmacological, non-anesthetic properties conferring cardiac protection and influencing perioperative and long term clinically relevant outcomes. Meta-analyses offer a quick and cheap method to improve clinical decision making. However, head-to-head treatment comparisons are not always available or conclusive. In this case network meta-analysis [1-3] can provide estimates of treatment efficacy of multiple treatment regimens. In doing so, it is possible to establish which treatment is superior reaching, through indirect comparisons, reliable conclusions otherwise difficult to achieve. To perform a network meta-analysis, it is indispensable that the consistency equation ($\theta_{BC}=\theta_{AC}-\theta_{BA}$) is satisfied. This means that, if the AB and AC trials are comparable in effect modifiers (are similar), an indirect estimate for the true difference effect between the treatment B versus C (θ_{BC}) can be obtained from the direct estimates of A versus B (θ_{BA}) and from direct estimates of A versus C (θ_{AC}). Hence, it is important that the indirect estimate is not biased and that there is no divergence between the direct and indirect comparisons [1].

In this work, we carried out both a pair-wise and a Bayesian network meta-analysis to assess how anaesthetic drugs influence patients' survival after cardiac surgery. The advantage of the Bayesian approach is that it allows for the incorporation, into the random-effect model, of the between studies heterogeneity degree, including a prior distribution for it and overcoming the problems related to the choice of variance estimate methods in the "classical" inference.

The primary objective of this study was therefore to determine whether anaesthetic techniques (volatile-based anaesthesia versus total intravenous anaesthesia - TIVA) confer a survival advantage for patients undergoing cardiac surgery. A secondary aim was to explore whether a

specific volatile (desflurane, isoflurane or sevoflurane) or TIVA agent is associated with an improved survival.

Methods

Pertinent studies were independently searched in BioMedCentral, MEDLINE/PubMed, Embase, and the Cochrane Central Register. Literature searches were last updated to June 1st 2012. No language restriction was enforced. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment and comparison between a TIVA and an anaesthesia plan including administration of isoflurane, desflurane or sevoflurane or a comparison between volatile agents, performed in cardiac surgical patients with no restriction in dose and time of administration. The exclusion criteria were duplicate publications, nonhuman experimental studies and lack of outcome data.

The standard pair-wise meta-analysis was performed in compliance with The Cochrane Collaboration standards [4]. The internal validity was critically evaluated judging the risk of selection-, performance-, attrition-, detection- and reporting-bias of each trial included. The evidence of publication bias was assessed by Peters regression asymmetry test and Begg adjusted-rank correlation test. A nonparametric trim-and-fill rank-based technique was also performed. Heterogeneity between studies was evaluated using the p-value from the Cochran Q statistic and the inconsistency index (I^2) [4]. Mortality data from individual studies were analyzed in order to compute pooled OR with pertinent 95% confidence intervals (CI), using the inverse of variance method with a fixed-effect model in case of low statistical inconsistency ($I^2 \leq 25\%$) or using the DerSimonian-Laird method with a random-effect model.

In the Bayesian network meta-analyses [2,3], each arm of the trials was classified according to its primary treatment strategy: 1) TIVA, 2) isoflurane, 3) desflurane and 4) sevoflurane. To assess the consistency assumption (no discrepancy between direct and indirect comparisons) we proposed and implemented the posterior probability check method [5] to compare the difference in residual deviance between the consistency model (which the indirect treatment effects by consistency equation) with the inconsistency one (which estimates all the relative effects for all the treatment contrasts).

The network analysis was carried out modeling the binary outcome mortality with a Bayesian hierarchical model (binomial model with logit link function) using a Markov chain Monte Carlo (MCMC) approach. We used non-informative priors (Normal distribution with mean equal to 0 and variance equal to 0.0001)to produce the posterior distributions for the treatment effect in the reference group (TIVA) and the treatment difference effects. To overcome the zero-cell count problem, we ran the random-effect model with a more informative prior (Inverse-Gamma distribution) on the variance parameter [3]. Pooled ORs were estimated from the mean of the posterior distribution obtained with the Bayesian approach.

After confirming the consistency hypothesis [6], the indirect estimate was calculated as difference from the appropriate direct estimates; the corresponding 95% credibility interval (CrI) was obtained by normal approximation. We considered models where the between trials variance is homogeneous across treatment contrasts. We took into account the correlation between the treatment difference effect for each group of multi-arm trials. We selected the fixed-effect model, which assume the between trials variance equal to zero, or the random-effect model, which assumes a different underlying effect for each study, calculating the posterior mean of the residual deviance (Dres) and the Deviance Information Criterion (DIC) statistic [3]. To explore the relation between log-risk of mortality and the length of study

follow-up, we performed a Bayesian meta-regression analysis. Sensitivity analyses were performed by analyzing data from studies with a low risk of bias, or by sequentially removing each study from the overall dataset, or by changing priors.
The statistical analysis was performed by STATA (release 11, College Station, TX) and winBUGS (release 1.4, freeware available by BUGS project).

Results

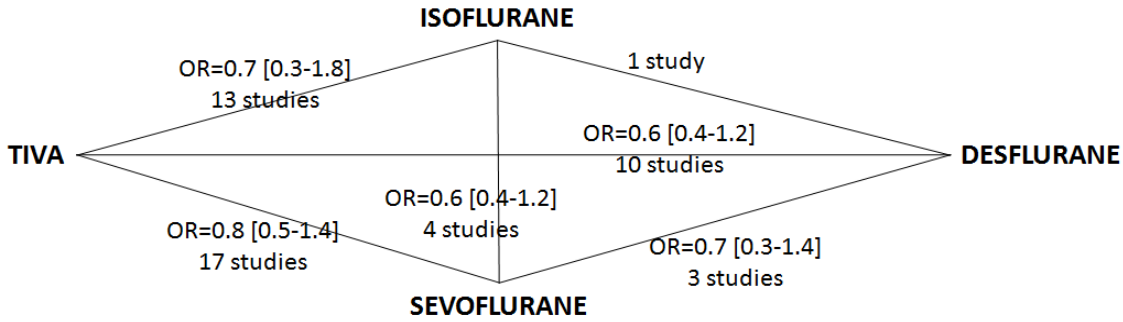
Database searches, snowballing and contacts with experts yielded a total of 2630 citations. Excluding 2518 non-pertinent titles or abstracts, and other 74 studies because of their non-experimental design or because of duplicate publications, we identified 38 eligible randomised clinical trials (all the study references are available from the authors).
The 38 included trials randomized 3,996 patients including 1,648 (41%) receiving TIVA and 2,348 (59%) receiving volatile agents. In details 622 (16%) patients received isoflurane, 701 (17%) received desflurane and 1,025 (26%) received sevoflurane. The trials included a median of 60 (range 20-414) randomised patient and were published between 1991 and 2012. Clinical heterogeneity was mostly due to control treatment and follow-up duration (median: 14 days, range: from 4 hours after surgery to 1 year). Figure 1 reports the network configuration and results from the standard meta-analyses on each contrast.
The overall standard meta-analysis showed that the use of volatile agents (isoflurane, desflurane, or sevoflurane) was associated with a reduction in mortality when compared to TIVA at the longest follow-up available (25/1994 [1.3%] in the volatile group versus 43/1648 [2.6%] in the TIVA arm, OR=0.51, 95% CI 0.33-0.81, p for effect =0.004, p for heterogeneity =0.9, I^2=0% with 35 studies included). Visual inspection of funnel plot did not identify an important skewed or asymmetrical shape. Since the quantitative evaluation suggested a possible presence of publication bias, as measured by Peters' test (p=0.02) and Begg' test (p=0.18), we used the trim-and-fill approach to confirm the results of our meta-analysis after adjusting for the presence of unpublished studies (OR=0.42, 95% CI 0.28-0.64, p for effect <0.001, p for heterogeneity =0.9, I^2=0%, with 13 studies added).
In the Bayesian network meta-analysis, the fit of the fixed- (Dres=127.5 and DIC=149.4) and random- (Dres=126.5 and DIC=150.1) effects models was similar. Hence, we selected the former model, which provided a slight increase in precision. We confirmed the consistency assumption (probability in favors of inconsistency model equal to 0.03). The results showed that the use of sevoflurane (posterior mean of OR =0.31, 95% CrI 0.14-0.64) and desflurane (posterior mean of OR =0.43, 95% CrI 0.21-0.82) was associated with a reduction in mortality when compared to TIVA at the longest follow-up available. When the largest trial was removed, we found that only the use of desflurane was associated with a significant reduction in mortality respect to TIVA (posterior mean of OR =0.30, 95% CrI 0.09-0.88). Furthermore, Bayesian meta-regressions of average follow-up against log-risk of mortality showed no significant effect for time on mortality (regression coefficient =-0.0008, CrI -0.004 to 0.002). The calculation of the posterior distribution of the probability to be the best and the worst, revealed a trend of TIVA to be the worst in terms of long survival after cardiac surgery. The sensitivity analysis did not show differences in the magnitude of effects.

Discussion

The present work shows that volatile anesthetics improve survival in cardiac surgery when compared to TIVA. No evidence-based data exist to suggest that one volatile agent (isoflurane,

desflurane, or sevoflurane) is more beneficial than the others, but there is initial evidence suggesting that TIVA is detrimental when compared to desflurane and sevoflurane.
Several limitations are acknowledged. Bayesian network meta-analysis incorporates both the direct and indirect comparisons between treatments. However, indirect evidence is susceptible to confounding and thus should be interpreted with caution since it does not always agree with the corresponding direct estimates. Although the consistency hypothesis was not rejected, additional methodological and empirical work needs to be done to evaluate the direct and indirect comparisons across a different types of interventions. Furthermore, Bayesian network meta-analyses assume that patients enrolled in the individual studies could have been sampled from the same theoretical population, and that similar comparators between different trials have a consistent risk-benefit ratio. Traditional limitations of meta-analyses (i.e. variations in the treatment regimens, in the populations or major subgroups within trials or in the conduct of the studies) apply to Bayesian network meta-analysis too. In particular, by removing the largest trial from the meta-analysis, only the use of desflurane was still associated with a significant reduction in mortality as compared to TIVA. Since the evidence comes from small RCTs, it is imperative to conduct a large, multicenter trial to confirm that survival is significantly influenced by the choice of the anesthetic.

Figure 1: Network configuration. Head-to-head comparisons and number of studies for each contrast.



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