Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 589–594 doi:10.1111/j.1365-2044.2009.05896.x

# Meta-analysis on the effect of dopexamine on in-hospital mortality

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## Summary

The objective of the study was to determine whether dopexamine alters in-hospital mortality. The following databases were searched, Embase (1974–July 2007), Medline (1950–July 2007), CINAHL, PubMed and Cochrane Clinical Register of Controlled Trials (CENTRAL). Two reviewers independently checked the quality of the studies and extracted data. Six randomised controlled trials totalling 935 patients were included. Mortality was not significantly different with dopexamine treatment (relative risk 0.75, 95% confidence interval 0.48–1.18, p = 0.22). In conclusion, dopexamine does not improve in-hospital mortality in patients undergoing major abdominal surgery and in the critically ill.

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*Accepted: 14 January 2009*

Dopexamine hydrochloride is a synthetic catecholamine with agonist effects at the dopamine 1 and 2 receptors. It is only one-third as potent as dopamine in stimulating the dopamine-1 receptor but has potent $\beta_2$ receptor agonist properties (60 times more potent than dopamine) and a weak $\beta_1$ receptor agonist effect [1]. It inhibits the reuptake (uptake-1) of noradrenaline but has no direct alpha activity [2]. These unique pharmacological features translate into a clinical profile of afterload reduction, direct and indirect positive inotropism and potentially both renal and splanchnic vascular bed dilatation [2]. The other suggested benefits include anti-inflammatory properties and a protective effect on hepato-cellular function [3]. Hence, dopexamine is widely used to improve renal and splanchnic perfusion both in the peri-operative and the critical care setting.

So far, clinical trials investigating the effects of dopexamine as an agent used to maximise oxygen delivery ($DO_2$) in the peri-operative period have yielded conflicting results. No large randomised controlled clinical trials (RCTs) have evaluated the survival benefit of dopexamine in major abdominal surgery or critical care. A recent systematic review analysed only the effect of dopexamine on renal and splanchnic perfusion [4]. Pearse et al. [5] have recently published an independent patient data meta-regression analysis involving only the studies conducted in patients undergoing major surgery. Our analysis includes all the studies in the analysis by Pearse et al. as well as a critical care study. An aggregate patient data meta-analysis was conducted to evaluate the effect of dopexamine on mortality.

## Methods

### Search strategy

The Medline (1950–July 2007), Embase (1974–July 2007), CINAHL, PubMed and Cochrane Clinical Register of Controlled Trials (CENTRAL) databases were searched for prospective, randomised controlled clinical trials (RCTs) comparing dopexamine with control in adult patients. The MeSH term 'dopexamine' anywhere in an article was searched (including title, abstract, text and references). The reference lists of the related reviews and original articles were also manually searched. The grey literature (e.g. abstracts and posters presented in various conferences) was also included in this comprehensive search.

### Selection and validity assessment

Only randomised controlled trials performed on adults where dopexamine was compared with a placebo or

control were included in this meta-analysis. Paediatric studies, animal studies and studies that were not in English were excluded. The abstracts of the studies were independently analysed by two reviewers (DJ, SG) to confirm the fulfilment of inclusion criteria. Two reviewers (DJ, SG) independently recorded the trial characteristics and abstracted data on a pre-designed data abstraction form. The Jadad scale was used to score the study quality [randomisation, method of randomisation, double blinding, method of double blinding and withdrawals and drop outs (0–5)] [6]. Allocation concealment and intention to treat analysis were also described using the Cochrane approach. There was no disagreement between the authors on study inclusion, data extraction and quality scoring.

### Statistical analysis

The data were combined to represent one large trial and was entered into REVMAN 4.2 (The Cochrane Collaboration, Oxford, UK, 2003) for analysis. The primary outcome chosen for the analysis was all cause hospital mortality.

The random effects model of DerSimonian and Laird [7] was used and the difference in outcome between the study and the control groups was reported as relative risks (RR) with 95% confidence intervals (CI). The heterogeneity between the included studies was assessed using the Cochrane $Q$ test with a $p \leq 0.10$ indicating heterogeneity [8, 9]. The $I^2$ statistic which is the proportion of total variation among studies that is explained by heterogeneity rather than chance was also reported [8, 9]. Substantial heterogeneity exists when $I^2$ exceeds 50%. Publication and other related bias was assessed by using the funnel plot of standard error against treatment effect. The funnel plot is based on the fact that precision in estimating the underlying treatment effect will increase as the sample size of component studies increases. Results from small studies will scatter widely at the bottom of the graph. The spread will narrow as precision increases among larger studies. In the absence of bias, the plot should thus resemble a symmetrical inverted funnel [10].

## Results

Six out of 42 potentially eligible studies, with a total of 935 patients, met the inclusion criteria (Fig. 1). Five of them were conducted in surgical patients who underwent major gastro-intestinal, urological and vascular surgery [11–15]. One study was conducted among patients in the intensive care unit [16]. All cause mortality (whether 28 day or in-hospital) was the primary outcome in four studies with the remaining two having other clinical primary outcomes with mortality or survival being assessed as one of the secondary outcomes. A large multicentre study performed by Takala et al. [13] compared two different doses of dopexamine (0.5 and 2 $\mu g.kg^{-1}.min^{-1}$) with control. It was included in the analysis as one study. The doses of dopexamine used in the studies varied widely from 0.125 to 2.0 $\mu g.kg^{-1}.min^{-1}$. The dose of dopexamine infusion was increased in a stepwise fashion to achieve a target oxygen delivery in three of the six studies. Four studies had a Jadad score of 3 or more with two studies scoring one and two out of the possible five (Table 1).

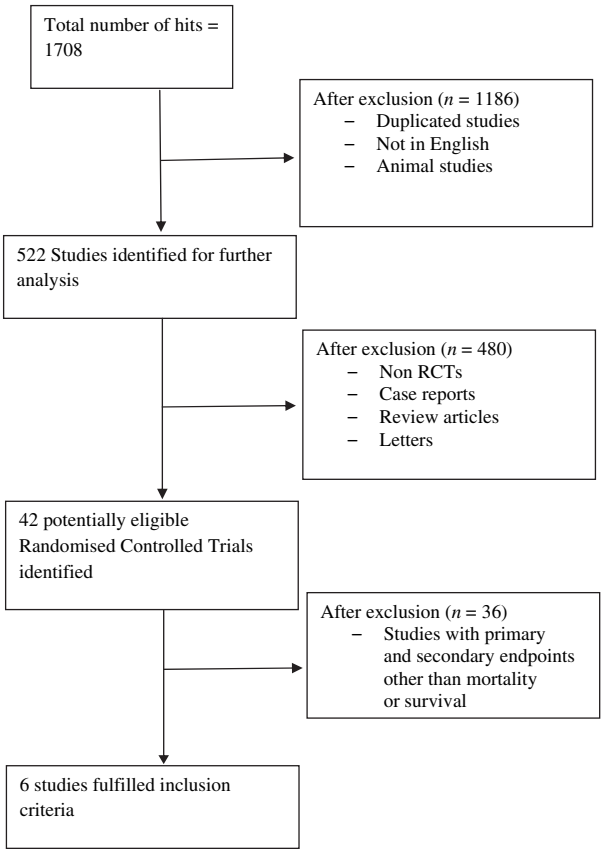


**Figure 1** Flow of studies in meta-analysis.

The study performed by Takala et al. [13], a large multicentre study consisting of 412 patients, contributed the largest number of patients and the study performed by Ralph et al. [16], a critical care study, contributed the greatest number of events to the pooled analysis. Both these studies found no effect on mortality.

The Cochrane $Q$ test was not significant with a p value of 0.13 and the $I^2$ value of 42% indicating moderate heterogeneity between the studies (Fig. 2).

The funnel plot of standard error against treatment effect is asymmetrical (Fig. 3). This indicates the presence of publication and other related bias including English language bias, citation bias and database bias.

**Table 1** Characteristics of studies included in the meta-analysis.

| Study | Participants | Interventions | Outcomes | Study quality |
|---|---|---|---|---|
| Boyd et al. [11] | 107 patients undergoing major abdominal or vascular procedures | 54 patients received standard pre-operative care; 53 patients received dopexamine infusion starting at 0.5 $\mu g.kg^{-1}.min^{-1}$ (mean pre-op 1.18 $\mu g.kg^{-1}.min^{-1}$; mean postop 1.32 $\mu g.kg^{-1}.min^{-1}$) | Mortality at 28 days and morbidity | Randomised but method of randomisation is not clearly specified, non-blinded, drop-outs not clearly described; Jadad score 1/5 |
| Stone et al. [12] | 100 patients undergoing major abdominal and urological procedures | 50 patients received saline (control) and 50 patients received dopexamine at 0.25 $\mu g.kg^{-1}.min^{-1}$ | Primary outcome was incidence of postoperative morbidity and outcome after surgery | Randomised, (computer generated), double-blinded, drop-outs withdrawals not described; Jadad score 4/5 |
| Takala et al. [13] | 412 patients undergoing major abdominal surgery | Control group ($n$ = 140) received standard intervention; study group 1 ($n$ = 135) received dopexamine 0.5 $\mu g.kg^{-1}.min^{-1}$; study group 2 ($n$ = 137) received dopexamine 2 $\mu g.kg^{-1}.min^{-1}$ | Mortality at 28 days postoperatively | Randomised, method of randomisation described, double-blinded, drop-outs clearly described; Jadad score 5/5 |
| Wilson et al. [14] | 138 patients undergoing general, vascular and urological procedures | Control group ($n$ = 46) received routine treatment; study group 1 ($n$ = 46) received adrenaline infusion; study group 2 received dopexamine 0.125 $\mu g.kg^{-1}.min^{-1}$ | In-hospital mortality and morbidity | Randomised, adequate allocation concealment, blinded; drop-outs not clearly described; Jadad score 3/5 |
| Pearse et al. [15] | 122 patients undergoing general surgery | Control = 60; goal directed therapy = 62; in the study group 55/62 patients received dopexamine (max. dose ≤ 1 $\mu g.kg^{-1}.min^{-1}$) and in the control group 1/60 received dopexamine | Primary outcome was incidence of postoperative complications; secondary outcome was morbidity and mortality | Randomisation and method of randomisation are satisfactory; it is a partly blinded study; drop-outs clearly described; Jadad score 3/5. |
| Ralph et al. [16] | 102 critically ill patients | Treatment group $n$ = 52; dopexamine was started at a dose of 0.5 $\mu g.kg^{-1}.min^{-1}$ and the dose was increased every 30 min (max 2.0 $\mu g.kg^{-1}.min^{-1}$; majority tolerated 2.0 $\mu g.kg^{-1}.min^{-1}$); control group $n$ = 50 | Primary outcome was gastro-intestinal permeability difference; secondary outcome was hospital survival | Randomised, method not described; non-blinded; drop-outs described; Jadad score 2/5 |

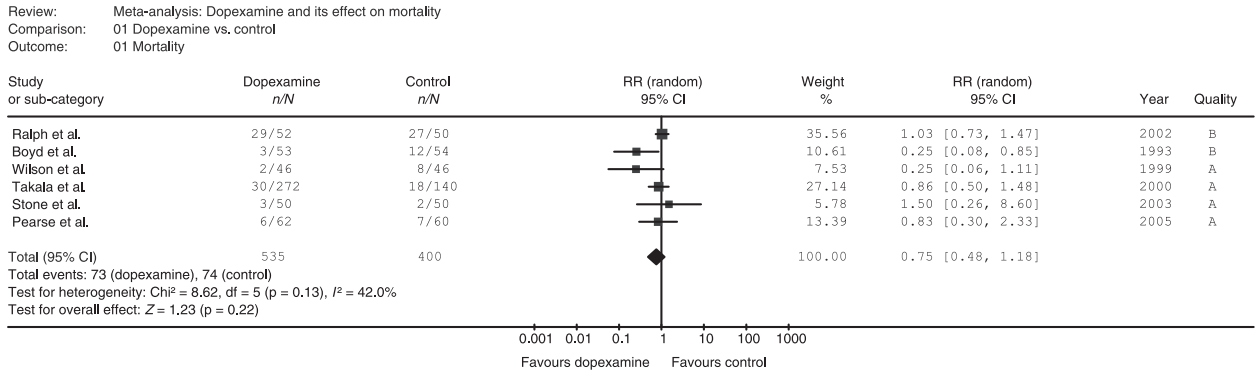


**Figure 2** Effect of dopexamine on mortality.

## Subset analysis

Takala et al. [13] randomised 412 patients into three groups, placebo ($n$ = 140) dopexamine 0.5 $\mu g.kg^{-1}.min^{-1}$ ($n$ = 135) and dopexamine 2 $\mu g.kg^{-1}.min^{-1}$ ($n$ = 137). In this study dopexamine had no effect on postoperative mortality in high risk patients undergoing major abdominal

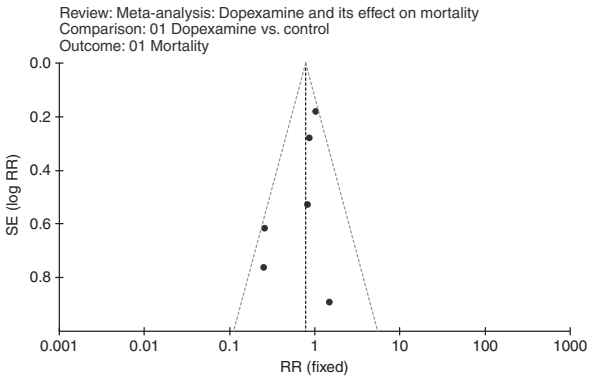


**Figure 3** Funnel plot of standard error against treatment effect.

surgery. However a post hoc analysis revealed a trend towards lower mortality in the low dose dopexamine group. We therefore decided to explore this relationship further and performed a subset analysis to determine the pooled estimate of mortality in those patients who received low dose dopexamine ($\leq 1$ $\mu g.kg^{-1}.min^{-1}$).The results failed to show any benefit (589 patients; RR 0.62; 95% CI 0.37–1.06; p = 0.08) (Fig. 4).

## Discussion

This meta-analysis identified six randomised controlled trials with a total of 935 patients. Methodologic quality of the trials varied and the trials were performed in differing patient groups. The results of this meta-analysis revealed that dopexamine does not improve in-hospital mortality in patients undergoing major surgery or in the critically ill. However, a wide 95% CI of 0.48–1.18 does not totally exclude a clinically important benefit (Fig. 2). The large multicentre trial conducted by Takala et al. [13] dominates the analysis because of its large sample size. This may lead to a criticism that this meta-analysis may reflect the result of that trial. Sensitivity analysis showed that the results did not change significantly when that trial was excluded from the analysis (RR = 0.66; 95% CI 0.33–1.31; p = 0.23). The trial performed by Pearse et al. [15] had dopexamine in the control group as well as treatment group. Also, in that trial, only 55 out of the 62 patients in the treatment group received dopexamine. Sensitivity analysis after omitting that study, did not alter the results significantly (RR of 0.71, 95% CI 0.41–1.23, p = 0.23).

One critical care study performed by Ralph et al. [16] was included. In that study the authors assessed the hospital survival in patients who received dopexamine (secondary outcome measure). The event rates in this study are much higher (hence, an increased weight) when compared to the other studies. It may be argued that this might swing the results against dopexamine. However sensitivity analysis clearly showed that dopexamine has no beneficial effect in surgical patients after the omission of this critical care study from the analysis (RR = 0.63; 95% CI = 0.35–1.13, p = 0.12).

The quality of the studies varied from 1/5 to 5/5 (Jadad scale). Four out of the six studies scored 3 or more on the Jadad scale indicating that the majority of the studies are of good quality. Sensitivity analysis was performed by excluding the studies that had low Jadad scores [11, 16]. The result was an RR of 0.79 (95% CI 0.49–1.26, p = 0.31). Hence, it can be safely concluded that the inclusion of low quality studies in our meta-analysis did not alter the result significantly.

The $I^2$ test revealed moderate heterogeneity between the studies. However it was decided to proceed with the analysis because, to date, there is no strong evidence to suggest for or against the use of dopexamine. Furthermore, exploring heterogeneity increases the strength of the conclusions drawn [17]. There are a number of reasons for heterogeneity identified in this meta-analysis including age difference (47–80 years), gender difference (more males than females overall), different treatment protocols used (0.125–2.0 $\mu g.kg^{-1}.min^{-1}$), varying duration of infusion of dopexamine and the varying qualities of the included studies (Jadad score 1/5–5/5).

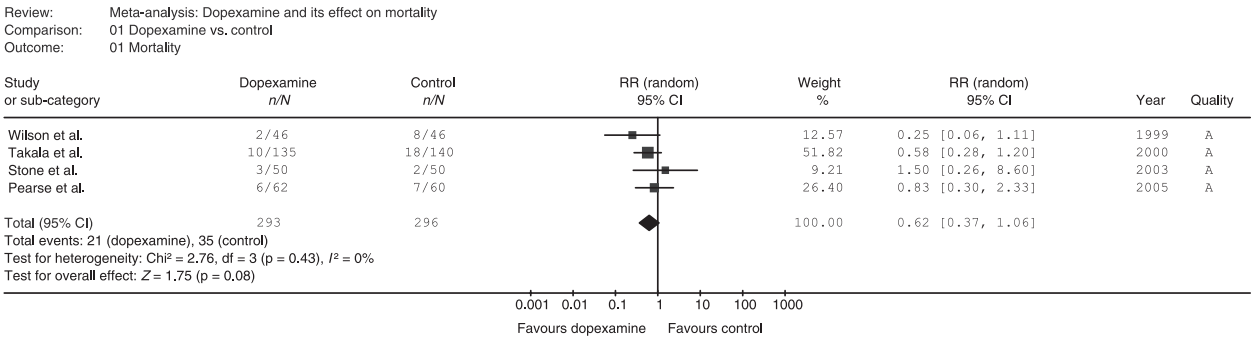


**Figure 4** Effect of low dose dopexamine ($\leq 1$ $\mu g.kg^{-1}.min^{-1}$) on mortality.

An independent patient data meta-regression analysis has recently been published by Pearse et al. [5]. There are significant differences between his analysis and ours. Firstly, the paper published by Pearse included only studies carried out in patients undergoing major surgery [5]. Our review includes the peri-operative studies and a critical care study. In clinical practice, in addition to peri-operative use, dopexamine is still widely used on the intensive care unit. Therefore, the inclusion of the critical care study is justified. Secondly, there is a difference in scoring the included trials. Pearse et al. [5] scored the study performed by Boyd et al. [11] as three or more on the Jadad scale. This study [11] was scored by us as only 1 out of the possible 5 points. It was scored on the Jadad scale as previously described after an independent assessment by both the authors (DJ, SG). This emphasises the fact that scoring systems may be subject to inter-observer variation. Furthermore there are differences in the analysis and the results between this study and that of Pearse et al. Our analysis is an aggregate patient data meta-analysis whereas the analysis performed by Pearse et al. [5] is an individual patient data meta-regression analysis.

When comparing the low dose dopexamine subset analysis in this study with the 28 day mortality intention to treat analysis in the study by Pearse et al. [5] significant differences are highlighted. There are differences in the event rates in the dopexamine and control groups between the two analyses. This is due to the fact that our study included all cause (in-hospital) mortality as the primary outcome measure whereas the study by Pearse et al. included only 28 day mortality. Therefore patients who died after 28 days are not included in the event rates in Pearse's analyses. However the difference in event rates between the two studies is relatively minor and by itself is unlikely to alter the summary estimate between the two analyses significantly. The most significant difference overall between the two analyses is the inclusion in Pearse's analysis of the study by Boyd et al. [2]. Our analysis is an aggregate patient data meta-analysis based only on the published data. The mean dopexamine use in the study by Boyd et al. [11] was 1.18 $\mu g.kg^{-1}.min^{-1}$ (SD 0.16) pre-operatively and 1.20 $\mu g.kg^{-1}.min^{-1}$ (SD 0.21) postoperatively. This study was therefore not included in the subset analysis on low dose dopexamine. Pearse et al. [5] had access to individual patient data for all the included studies and were therefore able to include a subset of patients from the Boyd paper who received low dose dopexamine. Whilst this is potentially a major advantage as it provides a more robust summary estimate, it is possible that the inclusion of a low quality study (Boyd study) may dilute this effect. The Boyd study was scored as 1 out of 5 on the Jadad score in our analysis. Furthermore the event rate in the control group was 12/54 and 0/27 in the dopexamine group [5]. This skews the result strongly in favour of dopexamine. It is therefore possible that the inclusion in Pearse's analysis of a low quality study with a relatively high event rate in the control group and a strong positive in favour of dopexamine has had the effect of skewing the overall summary estimate in favour of dopexamine.

It has been argued that individual patient data meta-regression analysis is superior to an aggregate data meta-analysis [18]. However in our analysis the lack of availability of individual patient data led to the exclusion in a subset analysis of a low quality study. This may have resulted in a more robust and valid summary estimate. From their analysis Pearse et al. [5] concluded that low dose dopexamine improves mortality and duration of hospital stay in patients undergoing major surgery. The results of our analysis do not support such a conclusion.

### Possible limitations of this meta-analysis

By performing a comprehensive and thorough literature search we minimised the risk of missing published clinical trials. In spite of this extensive search, it is still possible that we may not have identified all available published trials. As with any other meta-analysis, bias is a possible factor in our review. It is well known that study quality can affect the magnitude of the effect of a particular intervention [19]. In our meta-analysis, two low quality studies were included which might have affected the magnitude of the effect of dopexamine. Furthermore our analysis included small trials, the majority of which had low event rates. This might reduce the precision of the pooled estimate of mortality. Finally the result of our meta-analysis is based upon studies with a moderate degree of between-study heterogeneity. The asymmetry seen in the funnel plot could be the result of the small number of studies included in this meta-analysis as well as true publication bias. English language bias, citation bias and database bias may also be contributing factors.

## Conclusion

There is insufficient evidence to state conclusively that dopexamine reduces mortality. Although the results of this meta-analysis were largely consistent across the studies included, significant between study differences were found and only a limited number of studies are available for analysis. Finally whatever the strengths and limitations of this analysis compared to that of Pearse et al., the fact that two independent reviews have essentially examined similar data and arrived at different conclusions must serve to strengthen the argument for further high quality,

randomised controlled trials, comparing dopexamine and control, to address the fundamental question on the efficacy of dopexamine.

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