Dopexamine and its role in the protection of hepatosplanchnic and renal perfusion in high-risk surgical and critically ill patients

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Background. Dopexamine is increasingly being used in high-risk surgical and critically ill patients to preserve hepatosplanchnic and renal perfusion. This systematic review of randomized controlled trials was undertaken to investigate the clinical evidence for using dopexamine in this role.

Methods. Data sources included Medline, Cochrane Library, EMBASE and CINAHL and reference lists of relevant articles. Randomized controlled trials which compared dopexamine treatment with a control group, in high-risk surgical and critically ill adult patients and with primary outcome measures designed to assess hepatosplanchnic and renal perfusion were included. Articles not published in English were excluded.

Results. Twenty-one trials were selected from the literature search. The results suggest that dopexamine may protect against colonic mucosal damage in patients undergoing abdominal aortic surgery and may improve gastric mucosal pH in general surgical patients, especially those with preoperative gastric mucosal pH measurements <7.35 and those undergoing pancreaticoduodenectomy surgery. Dopexamine may have beneficial effects on renal perfusion in patients undergoing cardiac surgery but appears to have little or no benefit on gastric mucosal pH in the same patient population. In critically ill patients none of the studies demonstrated a beneficial effect of dopexamine on either hepatosplanchnic or renal perfusion.

Conclusion. The evidence provided by the existing studies is both inadequate and inconsistent. There is insufficient evidence to offer reliable recommendations on the clinical use of dopexamine for the protection of either hepatosplanchnic or renal perfusion in high-risk surgical patients. Furthermore, there is no current evidence to support a role for dopexamine in protecting either hepatosplanchnic or renal perfusion in critically ill patients.


Keywords: circulation, renal; circulation, splanchnic; complications, critically ill patients; review, systematic; surgery, cardiac; surgery, major; surgery, vascular; sympathetic nervous system, dopexamine

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Patients undergoing major surgery are at risk of developing postoperative complications resulting in increased mortality and morbidity, delayed recovery and longer duration of hospital stay. The risk is even greater in patients with multiple preoperative comorbidities, creating a subset of patients who comprise a particularly high-risk group. Similarly, critically ill patients are at increased risk of complications due to illness severity. The aetiology of these complications is multifactorial, but it has been suggested that hepatosplanchnic and renal ischaemia may be significant contributing factors.1 Attention has now focused on developing a therapeutic agent or intervention that may protect these organs by preserving perfusion and preventing the development of tissue ischaemia.

Dopexamine hydrochloride is a synthetic catecholamine with marked intrinsic agonist activity at β2 adrenergic receptors, less agonist activity at DA1 dopaminergic receptors and weak agonist activity at β1 adrenergic and DA2 dopaminergic receptors. In addition, dopexamine exhibits indirect sympathomimetic actions mediated by inhibition of neuronal uptake of endogenous catecholamines but it is devoid of any intrinsic action at α adrenergic receptors.2 The primary
indication for dopexamine is as a positive inotrope and vasodilator for use in acute exacerbations of chronic heart failure and in heart failure associated with cardiac surgery. However, it has also been proposed that the unique receptor activity of dopexamine may make it effective in countering the vasoconstriction that occurs within the hepatosplanchnic and renal microcirculations during times of physiological stress. In this context, dopexamine may be the ideal agent to protect perfusion to the hepatosplanchnic and renal organs, thereby minimizing ischaemic tissue damage and subsequent organ dysfunction in these high-risk groups.

The aim of this systematic review is to evaluate the evidence for the role of dopexamine in preserving both hepatosplanchnic and renal perfusion in high-risk surgical and critically ill patients.

**Methods**

Relevant primary research relating to the use of dopexamine was identified by searching a number of electronic databases including Medline (1966–May 2003), the Cochrane Library, EMBASE (1980–week 21, 2003) and CINAHL. The databases were searched using dopexamine as a keyword and medical subject heading (MeSH). All citations identified by this search strategy were screened, and those considered relevant to the review were imported into the computer software program Reference Manager 10. Finally, the reference lists of all relevant literature were reviewed to identify additional papers not indexed in the databases. Studies were selected for inclusion in the review based on the following criteria: a study population of intensive care patients or patients undergoing major surgery, dopexamine infusion as an intervention, outcome measures relating to renal and hepatosplanchnic perfusion and a randomized controlled study design. Papers that were not published in English, trials with no control group, trials with neonates or infants as the study population and articles without full journal publication were excluded. All studies were critically appraised and scored for methodological quality using a modified scoring system described by Heyland and colleagues (Table 1). The maximum score awardable was 11. The study designs and outcome variables were too heterogeneous to allow statistical analysis of pooled data; therefore results were compared and contrasted using descriptive analysis.

**Results**

A total of 351 articles were identified using the search profile described above. Of these, 35 papers reported clinical trials investigating the effect of dopexamine on hepatosplanchnic or renal perfusion in major surgical or critically ill patients. Eight of these trials were excluded because no randomization method was reported, and a further six were excluded because there were no control groups for comparison. Of the final 21 studies included in the review, 15 investigated hepatosplanchnic perfusion in patients undergoing major surgery, three investigated hepatosplanchnic perfusion in critically ill patients, four investigated renal perfusion in patients undergoing major surgery and one investigated renal perfusion in critically ill patients. The median quality score was 6 (range 2–10). The results are summarized in Tables 2–7.

**Dopexamine and hepatosplanchnic perfusion**

Three studies explored the effect of dopexamine on hepatosplanchnic perfusion in patients undergoing elective infrarenal aortic surgery (Table 2). Baguneid and colleagues, in a sidearm to a multicentre trial, performed pre- and postoperative colonoscopy and mucosal biopsies to assess the degree of colonic mucosal inflammation and ischaemia.
Dopexamine in high-risk surgical and critically ill patients

Table 2  Summary of studies investigating effect of dopexamine on hepatosplanchnic perfusion or function in vascular surgery patients

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score</th>
<th>Total no. patients</th>
<th>Study population</th>
<th>Treatment groups</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>10</td>
<td>24</td>
<td>Elective infrarenal abdominal aortic aneurysm repair</td>
<td>Dopexamine 0.5–2 μg kg⁻¹ min⁻¹ Saline Started after induction of anaesthesia Continued until end of surgery</td>
<td>Dual sugar absorption</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>18</td>
<td>9</td>
<td>30</td>
<td>Elective infrarenal aortic surgery</td>
<td>Dopexamine 2 μg kg⁻¹ min⁻¹ Saline Started after induction of anaesthesia Continued for 24 h</td>
<td>Colonoscopy and biopsy</td>
<td>Significantly less evidence of mucosal ischaemic changes in treatment group</td>
</tr>
<tr>
<td>19</td>
<td>5</td>
<td>20</td>
<td>Elective infrarenal aortic surgery</td>
<td>Dopexamine 1 μg kg⁻¹ min⁻¹ Saline Started after induction of anaesthesia Continued for 24 h</td>
<td>Gastric intramucosal pH</td>
<td>No significant difference between groups</td>
</tr>
</tbody>
</table>

There was a significant increase in the number of patients with histological appearance suggestive of mucosal ischaemia and in the degree of mucosal ischaemia in the control group compared with the dopexamine-treated group. However, there were no differences in the immunohistochemical markers of inflammation between the groups. In contrast, Piper and colleagues, in a small study of 20 patients, reported no beneficial effect on gastric mucosal pH·i following 24 h of dopexamine treatment, although three patients were excluded from analysis because of the use of additional catecholamines. This raises the possibility that dopexamine may have a differential effect on the perfusion of the intestinal mucosa, offering greater protection to colonic than to gastric mucosa in this particular patient population.

Mc Ginley and colleagues, in a small two-centre study, assessed postoperative gut permeability using the dual sugar absorption method and found it increased in all patients, including those randomized to receive dopexamine. Although well conducted, this trial limited the period of dopexamine treatment to the duration of surgery. This may be insufficient time for dopexamine to have any impact on mucosal integrity. Indeed, it is probable that the intestinal mucosa continues to be at risk of ischaemia well into the postoperative period and therefore would benefit from sustained protection during this time.

Seven trials explored the effect of dopexamine on hepatosplanchnic perfusion in patients undergoing major abdominal surgery (Table 3). Three studies measured gastric mucosal pH·i and one assessed mucosal to arterial PCO₂ gradient. Poeze and colleagues, in a side-arm to a large multicentre trial, performed a retrospective analysis of the gastric mucosal pH data from 286 patients. The results suggest that treatment with dopexamine is effective at raising gastric mucosal pH·i but only in those patients with preoperative readings <7.35. Similarly, Boldt and colleagues, in a well-conducted trial involving patients undergoing pancreatecto-duodenectomy surgery, reported a significant improvement in gastric mucosal pH·i in patients treated with dopexamine, although four control patients also received treatment with dobutamine. In contrast, Byers and colleagues reported no significant differences in gastric mucosal pH·i readings between patients treated with dopexamine and control patients, although this trial reported a high mortality rate in the control group. Muller and colleagues measured mucosal to arterial PCO₂ gradient but found no significant difference between treatment and control patients. However, dopexamine therapy was limited to only 1 h and two patients were excluded because of difficulties in obtaining mucosal PCO₂ estimates. Of the final three studies, Suojaranta-Ylinen and colleagues found no improvement in liver blood flow between treatment and control patients, measured using indocyanine green clearance. Bellamy and colleagues, in a cross-over study, found a significant improvement in mucosal blood flow, measured using laser Doppler flowmetry, and Kaisers and colleagues, also in a cross-over study, reported similar improvements in hepatic venous oxygen saturation in the presence of dopexamine.

Five trials investigated the effect of dopexamine on hepatosplanchnic perfusion in adult patients undergoing cardiac surgery (Table 4). Of these, three assessed the effect of dopexamine on gastric mucosal pH·i or mucosa to arterial PCO₂ gradient and reported no benefit from treatment with dopexamine. There were inconsistencies in these studies in that Berendes and colleagues included nine patients who received additional treatment with norepinephrine, and four patients were withdrawn from the study by Gärdebäck and Settergren because their mucosal PCO₂ was less than their arterial PCO₂, suggesting errors in measurement. Interestingly, the study by Gärdebäck and colleagues included only those patients who developed a low postoperative gastric mucosal pH·i but demonstrated no benefit. This contrasts with the work by Poeze and colleagues in abdominal surgery. The small cross-over trial by Thoren and colleagues suggested that dopexamine was effective at increasing mucosal blood flow, measured using laser Doppler flowmetry, but there was no comment on any improvement in mucosal oxygenation. Furthermore, the increase in
gut permeability or Sequential Organ Failure Assessment (SOFA) scores. Two cross-over studies by Blunt and colleagues\textsuperscript{34} and Trinder and colleagues\textsuperscript{35} found no improvement in gastric mucosal pH\textsubscript{i} in patients treated with dopexamine; however, the identification of a time effect in the second phase of both trials means that their results must be interpreted with caution.

In summary, the evidence available to assess the role of dopexamine in protecting hepatosplanchnic perfusion in surgical patients is inadequate and inconclusive. The validity of the clinical trials is affected by difficulties in measuring hepatosplanchnic perfusion and methodological flaws in the study designs. At best, dopexamine may improve gastric mucosal pH\textsubscript{i} in general surgery patients whose preoperative gastrointestinal endoscopy and biopsy Gastric pH\textsubscript{i} No significant difference between groups

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score</th>
<th>Total no. patients</th>
<th>Study population</th>
<th>Treatment groups</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>4</td>
<td>21</td>
<td>Major abdominal surgery lasting &gt;90 min and with at least one high-risk criterion Preoptimized with fluids</td>
<td>Dopexamine 0.5 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} Saline Started preoperatively Continued for 24 h postoperatively</td>
<td>ICG clearance</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>23</td>
<td>5</td>
<td>38</td>
<td>Major abdominal surgery lasting &gt;90 min and with at least one high-risk criterion Preoptimized with fluids</td>
<td>Dopexamine 0.5 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} Saline Started 2–12 h preoperatively Continued for 24 h postoperatively</td>
<td>Upper gastrointestinal endoscopy and biopsy Gastric pH\textsubscript{i}</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>21</td>
<td>6</td>
<td>286</td>
<td>Major abdominal surgery lasting &gt;90 min and with at least one high-risk criterion Preoptimized with fluids</td>
<td>Low pH\textsubscript{i} group and normal pH\textsubscript{i} group Within each group patients received either: Dopexamine 0.5 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} Saline Started 2–12 h preoperatively Continued for 24 h postoperatively</td>
<td>Gastric pH\textsubscript{i} MOF score</td>
<td>Low pH\textsubscript{i} group: significantly higher pH\textsubscript{i} postoperatively in patients receiving dopexamine 0.5 and lower MOF in all patients receiving dopamine High pH\textsubscript{i} group: no significant differences between groups</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>18</td>
<td>Major elective abdominal surgery</td>
<td>Dopexamine 1 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} Saline Started after abdomen opened Continued for 1 h</td>
<td>Tissue oxygenation Gastric mucosal–arterial $P_{\text{CO}_2}$ gap</td>
<td>No significant difference in $P_{\text{CO}_2}$ gap within or between groups</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
<td>30</td>
<td>Pancreatico-duodenectomy</td>
<td>Dopexamine 2 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} Saline Started after induction of anaesthesia Continued until first postoperative day</td>
<td>Gastric pH\textsubscript{i} Vasoactive mediators</td>
<td>Gastric pH\textsubscript{i} significantly higher and vasoactive mediators significantly lower in treatment group</td>
</tr>
<tr>
<td>26</td>
<td>5</td>
<td>5</td>
<td>Small bowel transplantation</td>
<td>Dopexamine 0, 1 and 2 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} In random order for 1 h each</td>
<td>Laser Doppler flowmetry</td>
<td>Correlation between dopexamine and mucosal perfusion</td>
</tr>
<tr>
<td>27</td>
<td>7</td>
<td>17</td>
<td>Orthotopic liver transplant</td>
<td>Dopamine 4 + 8 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} Dobutamine 5 + 10 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} Started 8 h postoperatively and given in random order for 35 min each</td>
<td>Hepatic vein oxygen saturation</td>
<td>Significant increase with all drugs</td>
</tr>
</tbody>
</table>

Blood flow was associated with a similar percentage increase in cardiac output, implying no specific vasodilatory effect of dopexamine on the hepatosplanchnic microcirculation. Sharpe and colleagues\textsuperscript{32} found no improvement in liver blood flow in patients treated with dopexamine at a dose of 1 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1} compared with control patients.

Three studies were identified that explored the role of dopexamine in preserving hepatosplanchnic perfusion in critically ill patients (Table 5). None of the trials reported any beneficial effect. However, this area of research is compounded by difficulties in defining what constitutes a critically ill patient, and all three studies used slightly different selection criteria that may have resulted in different study populations. The large trial by Ralph and colleagues\textsuperscript{33} included 102 patients and infused dopexamine over a prolonged period. Despite methodological flaws, the authors reported no benefit from treatment with dopexamine on gut permeability or Sequential Organ Failure Assessment.
undergoing cardiac surgery. Current evidence does not support the use of dopexamine in protecting hepatosplanchnic perfusion in critically ill patients.

**Dopexamine and renal perfusion**

Four studies explored the effect of dopexamine on renal hemodynamics and function in adult patients undergoing elective high-risk surgery (Table 6). Three trials involved patients undergoing cardiac surgery and one involved patients undergoing infrarenal abdominal aortic aneurysm repair. In those studies taking creatinine clearance as the primary outcome measure of interest, only one, by Berendes and colleagues, showed a significant benefit from treatment with dopexamine in patients undergoing cardiac surgery. Three of the four trials only included patients with normal preoperative renal function. However, Dehne and colleagues specifically included patients with preoperative renal impairment, an important patient group at risk of developing postoperative renal failure and in which a protective agent would be beneficial. This study failed to show any significant difference in creatinine clearance between treatment and control patients, with or without renal impairment. One potential reason for this negative result is that treatment was terminated at the end of surgery despite the likelihood that the renal organs continue to be at risk of ischaemia into the postoperative period and may benefit from ongoing protection during

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**Table 4** Summary of studies investigating effect of dopexamine on hepatosplanchnic perfusion or function in cardiac surgery patients. CABG, coronary artery bypass graft; ICG, indocyanine green

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score</th>
<th>Total no. patients</th>
<th>Study population</th>
<th>Treatment groups</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>6</td>
<td>14</td>
<td>Elective CABG</td>
<td>Dopexamine, dopamine and dobutamine in random order Started after surgery Trial period 3 h</td>
<td>Laser Doppler flowmetry</td>
<td>Significant increase in jejunal mucosal blood flow but not as a fraction of CO</td>
</tr>
<tr>
<td>32</td>
<td>6</td>
<td>30</td>
<td>Elective CABG</td>
<td>Dopexamine 1 and 2 μg kg⁻¹ min⁻¹ Dopamine 4 μg kg⁻¹ min⁻¹ Dextrose Started after surgery Continued for 1 h</td>
<td>Plasma clearance rate of ICG dye</td>
<td>No significant difference between or within groups</td>
</tr>
<tr>
<td>28</td>
<td>7</td>
<td>44</td>
<td>Elective CABG</td>
<td>Dopexamine 0.5, 1 or 2 μg kg⁻¹ min⁻¹ Saline Continued for 24 h</td>
<td>Hepatic venous oxygen saturation Gastric mucosal pH</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
<td>19</td>
<td>Elective cardiac valve surgery Gastric mucosal pHi &lt;7.30</td>
<td>Dopexamine 2 μg kg⁻¹ min⁻¹ Saline Started after surgery Continued for 18 h</td>
<td>Gastric mucosal pH pH gradient between gastric mucosa and arterial blood</td>
<td>pHi significantly lower in treatment group compared with placebo but no significant difference in pH gradient</td>
</tr>
<tr>
<td>29</td>
<td>2</td>
<td>35</td>
<td>Elective CABG or valve surgery</td>
<td>Dopexamine 1 μg kg⁻¹ min⁻¹ Dopamine 2.5 μg kg⁻¹ min⁻¹ No infusion Started after induction of anaesthesia Continued for 16 h</td>
<td>Gastric mucosal pH Pco₂ and pH gradient between gastric mucosa and arterial blood</td>
<td>No significant difference between groups</td>
</tr>
</tbody>
</table>

**Table 5** Summary of studies investigating effect of dopexamine on hepatosplanchnic perfusion or function in critically ill patients. SIRS, systemic inflammatory response syndrome

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score</th>
<th>Total no. patients</th>
<th>Study population</th>
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<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>4</td>
<td>102</td>
<td>Patients predicted to require ICU care for at least 4 days</td>
<td>Dopexamine 0.5–2 μg kg⁻¹ min⁻¹ No infusion Started after resuscitation Continued for 7 days</td>
<td>Dual sugar absorption Sequential Organ Failure Score</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>34</td>
<td>6</td>
<td>40</td>
<td>Patients with SIRS</td>
<td>Dopexamine 1.25 μg kg⁻¹ min⁻¹ and prostacyclin in random order Continued for 6 h with a 12 h rest period</td>
<td>Gastric mucosal pH</td>
<td>No significant difference before and after dopexamine</td>
</tr>
<tr>
<td>35</td>
<td>6</td>
<td>12</td>
<td>Patients with pHi &lt;7.32</td>
<td>Dopexamine 4–6 μg kg⁻¹ min⁻¹ plus colloid boluses Dextrose Continued for 3 h</td>
<td>Gastric mucosal pH</td>
<td>No significant difference between groups</td>
</tr>
</tbody>
</table>
The aims of this review were to evaluate the clinical evidence for the use of dopexamine. A comprehensive literature search was conducted to identify relevant studies and those satisfying the explicit selection criteria were analysed and discussed. The results suggest that dopexamine may protect colonic mucosa in patients undergoing abdominal aortic surgery and may improve gastric mucosal pH in high-risk surgical patients, specifically those whose preoperative gastric mucosal pH is <7.35, and in those undergoing pancreatectoduodenectomy surgery. It may also protect renal perfusion in patients undergoing cardiac surgery but appears to have little or no benefit on gastric mucosal pH in the same patient population. None of the studies suggested a beneficial effect of dopexamine on either hepatosplanchnic or renal perfusion in critically ill patients. Variations in outcome measures, study populations, treatment protocols and methodological quality created difficulties in combining study results. As a consequence the supporting information is inadequate to provide evidence-based clinical recommendations for the use of dopexamine.

Clinical measurement of the effect of treatment in this area of research is difficult. The hepatosplanchnic and renal circulations are complex systems comprising a number of vascular beds that react in different ways to physiological

### Discussion

There are sound theoretical reasons as to why dopexamine hydrochloride might be effective in maintaining adequate perfusion to both the hepatosplanchnic and renal organs in high-risk surgical patients and critically ill patients. The aims of this review were to evaluate the clinical evidence for this theory. A comprehensive literature search was conducted to identify relevant studies and those satisfying the explicit selection criteria were analysed and discussed. The results suggest that dopexamine may protect colonic mucosa in patients undergoing abdominal aortic surgery and may improve gastric mucosal pH in high-risk surgical patients, specifically those whose preoperative gastric mucosal pH is <7.35, and in those undergoing pancreatectoduodenectomy surgery. It may also protect renal perfusion in patients undergoing cardiac surgery but appears to have little or no benefit on gastric mucosal pH in the same patient population. None of the studies suggested a beneficial effect of dopexamine on either hepatosplanchnic or renal perfusion in critically ill patients. Variations in outcome measures, study populations, treatment protocols and methodological quality created difficulties in combining study results. As a consequence the supporting information is inadequate to provide evidence-based clinical recommendations for the use of dopexamine.

Clinical measurement of the effect of treatment in this area of research is difficult. The hepatosplanchnic and renal circulations are complex systems comprising a number of vascular beds that react in different ways to physiological

### Table 6 Summary of studies investigating effect of dopexamine on renal perfusion or function in surgical patients. CABG, coronary artery bypass graft

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score</th>
<th>Total no. patients</th>
<th>Study population</th>
<th>Treatment groups</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>5</td>
<td>32</td>
<td>Elective infrarenal abdominal aortic aneurysm repair Normal renal function</td>
<td>Dopexamine 2 μg kg⁻¹ min⁻¹ Saline Started after induction of anaesthesia Continued for 24 h</td>
<td>Serum creatinine Creatinine clearance</td>
<td>Serum creatinine increased in placebo group, no significant changes in creatinine clearance</td>
</tr>
<tr>
<td>36</td>
<td>6</td>
<td>48</td>
<td>Elective CABG</td>
<td>Normal renal function (control)</td>
<td>Serum creatinine Urine osmolality Urine proteins Creatinine clearance</td>
<td>No significant difference between groups, with or without pre-renal dysfunction</td>
</tr>
<tr>
<td>37</td>
<td>9</td>
<td>20</td>
<td>Elective CABG EF&gt;50% Normal renal function</td>
<td>Dopexamine 0.5, 1, 2 and 4 μg kg⁻¹ min⁻¹ Saline Started 1–3 h after admission to ICU Continued for 40 min at each dose</td>
<td>Renal vascular resistance index</td>
<td>Significant increase within both groups but no significant difference between groups</td>
</tr>
<tr>
<td>28</td>
<td>7</td>
<td>44</td>
<td>Elective CABG Normal renal function</td>
<td>Dopexamine 0.5, 1 or 2 μg kg⁻¹ min⁻¹ Saline Started after induction of anaesthesia Continued for 24 h</td>
<td>Creatinine clearance</td>
<td>Significant increase in creatinine clearance in treatment group</td>
</tr>
</tbody>
</table>

### Table 7 Summary of studies investigating effect of dopexamine on renal perfusion or function in critically ill patients

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score</th>
<th>Total no. patients</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>4</td>
<td>102</td>
<td>Patients predicted to require ICU care for at least 4 days</td>
<td>Dopexamine 0.5–2 μg kg⁻¹ min⁻¹ No infusion Started after resuscitation Continued for 7 days</td>
<td>Creatinine clearance</td>
<td>No significant difference between groups</td>
</tr>
</tbody>
</table>

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this time. One study measured the renal vascular resistance index and found no difference between patient groups, but the clinical implications of this are not known. The trial involving vascular surgical patients showed no improvement in creatinine clearance with dopexamine treatment.

Only one study investigated the effect of dopexamine on renal function in critically ill patients (Table 7). However, this trial provides no evidence that dopexamine protects renal function in the population investigated, even following prolonged infusion over several days.

In summary, one well-conducted study suggests that dopexamine may protect renal function in patients undergoing cardiac surgery with normal preoperative renal function. There is no current evidence to suggest a protective role in either vascular surgery patients or critically ill patients.
The efficacy of dopexamine appeared to vary between study populations with surgical patients generally showing greater benefit than critically ill patients. The nature and duration of physiological stresses may be sufficiently dissimilar between these two patient groups to impact on hepatosplanchnic and renal perfusion in different ways, thereby affecting response to treatment. Alternatively, the timing of treatment in relation to the physiological insult is likely to be an important factor. It is known that reperfusion following ischaemia is a major contributing factor in tissue damage and the prevention of ischaemia may be more important than reversing it once it has occurred. In surgical patients it is possible to initiate dopexamine therapy before any insult threatens hepatosplanchnic and renal perfusion, whereas in critically ill patients it is inevitably commenced after the physiological insult has occurred. This may partially explain the disappointing results seen in critically ill patients.

Surprisingly, there appeared to be no dose–effect relationship, but duration of therapy may be an important factor in the treatment response. It should be sufficiently long to allow time for improved splanchnic and renal perfusion to have an impact on tissue oxygenation. Poeze and colleagues found that 6 h of treatment with dopexamine was required before any significant impact on gastric mucosal pHi was seen, suggesting that this should be the minimum duration. In addition, it would seem logical that treatment should be continued until the perfusion of hepatosplanchnic and renal organs is no longer at risk of compromise. Therefore the optimum treatment regime remains far from clear.

Dopexamine causes vasodilation and this may unmask covert hypovolaemia, necessitating the use of additional volume expansion to maintain blood pressure. Therefore it is possible that patients receiving treatment may also have received excess fluids compared with control patients, and this could potentially explain some of the beneficial effects attributed to dopexamine. Despite the importance of fluid management, only eight out of 21 studies reported the volume and type of fluids given. However, all of these eight studies reported fluid volumes to be comparable between groups, suggesting that, in this context, fluids did not influence the results significantly. Similarly, comparison with other vaso dilators did not reveal any consistencies in results, suggesting that vasodilation and additional fluids alone cannot explain the potential benefits offered by dopexamine. More recent work suggests that dopexamine possesses anti-inflammatory properties and may potentially have a role to play in the modulation of the systemic inflammatory response syndrome (SIRS). However, whether this is due to a direct anti-inflammatory effect or is secondary to protection of gut perfusion and function remains far from clear.

Encouragingly, there was a low incidence of adverse effects associated with dopexamine treatment in the studies reviewed, with very few patients withdrawn from trials because of drug intolerance. The most common reason for terminating treatment was sinus tachycardia, although this was rarely associated with evidence of myocardial ischaemia. Other literature suggests that dopexamine treatment is associated with only limited increases in myocardial oxygen demand and a low risk of cardiac arrhythmias. Even so, tachycardia is generally considered undesirable in high-risk patients, particularly those with a history of heart disease, and this must be taken into consideration when deciding whether to use dopexamine in individual patients.

Flaws in study methodology further compound interpretation of results. There are many sources of bias that can threaten the internal validity of a clinical trial. Most can be minimized by appropriate randomization, use of control groups and blinding of treatment options; hence only randomized controlled trials were included in this review. Unfortunately, although studies stated that patients were randomized, the method used was often not adequately described and therefore appropriateness could not be ascertained. There is no proven alternative treatment for the protection of hepatosplanchnic and renal organs against which to compare dopexamine, thereby necessitating the use of a placebo control group. Several studies failed to include a control group and were therefore omitted from the review. Blinding of the investigator to treatment option is important in order to minimize assessment bias. Despite this, several trials were non-blinded and others did not make it clear whether or how blinding was achieved. Finally, many of the trials used small sample sizes with a median size of 30 subjects (range 5–286). Only two trials involved more than 50 subjects. Most studies did not justify the initial sample sizes used and several studies were underpowered.
In conclusion, the evidence provided by these studies is inadequate and inconsistent. As a result there is insufficient evidence to offer reliable clinical recommendations on the use of dopexamine for the protection of either hepatosplanchic or renal perfusion in high-risk surgical patients. There is no current evidence to support a role for dopexamine in protecting either hepatosplanchic or renal perfusion in critically ill patients.

References

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