A Comparison of Nitroglycerin and Nitroprusside for Inducing Hypotension in Children: A Double-blind Study

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Intravenous nitroglycerin (NTG) and sodium nitroprusside (SNO) were compared as hypotensive agents in anesthetized children and adolescents. The drugs were studied in a prospective, randomized, double-blind fashion in 14 patients anesthetized with nitrous oxide, oxygen, morphine, and thiopental. NTG in doses as high as 40 
\( \mu g \cdot kg^{-1} \cdot min^{-1} \) was ineffective at decreasing mean arterial pressure (MAP) below 55 mmHg or causing a decrease in MAP greater than one-third of baseline values. SNP was uniformly successful at inducing hypotension in all patients, including those patients in whom NTG failed. The dose of SNP required to induce hypotension was 6–8 
\( \mu g \cdot kg^{-1} \cdot min^{-1} \). Both NTG and SNP decreased systemic vascular resistance, although SNP did so to a much greater degree than NTG (64% vs. 29%; \( P < 0.01 \)). Only SNP increased cardiac index significantly (2.27 ± 0.35 to 4.44 ± 1.36; \( P < 0.003 \)). Both drugs reflexly increased heart rate, necessitating the use of intravenous propranolol (range from 1 to 5 mg) in all patients. Both drugs produced small decreases in arterial oxygen tension and increases in the average alveolar–arterial oxygen tension gradient (SNP, 44 ± 13 vs. NTG, 41 ± 0). SNP use was associated with a slight metabolic acidosis (pH = 7.38 ± 0.01; base excess [BE] = −6 ± 1). Neither drug produced any other untoward reaction. SNP appears to be the agent of choice for the reliable and sustained induction of deliberate hypotension in children and adolescents. (Key words: Anesthesia; pediatric; Anesthetic techniques: hypotension; nitroglycerin; nitroprusside.

DELIBERATE HYPOTENSION, as an adjunct to general anesthesia, provides a relatively bloodless surgical field, facilitates surgical dissection, and decreases operative time.\(^3\) Because it decreases the intraoperative blood loss, deliberate hypotension also diminishes the need for and the risks of blood transfusions. The drug most commonly used for this purpose is sodium nitroprusside (SNP),\(^4\) although in adults, intravenous nitroglycerin (NTG)\(^6\) is being used more frequently. In adults, NTG produces a smooth, gradual decrease in blood pressure and minimizes the danger of producing severe hypotension. It does not have the potential of cyanide toxicity, and tachyphylaxis has not been reported. As a result of these advantages over SNP, many anesthesiologists favor NTG use in adults undergoing deliberate hypotension. The use of NTG as a hypotensive agent in children has not been reported.

This double-blind, randomized study compared the efficacy and cardiovascular effects of intravenous NTG and SNP as hypotensive agents in children and adolescents under general anesthesia when the inhalational anesthetic halothane was discontinued. We elected not to use halothane as an adjunct to the induction of deliberate hypotension in this study because of its depressant effects on somatosensory-evoked potentials, which we routinely monitor in spinal surgery.\(^7\)–\(^10\)

MATERIALS AND METHODS

PATIENT SELECTION

Fourteen ASA Class I and II patients, 9 to 14 yr of age, scheduled for scoliosis, craniofacial, or hepatic surgery were studied. Approval was obtained from the Food and Drug Administration, the institution’s Joint Committee on Clinical Investigation, and the Department of Anesthesiology/Critical Care Medicine’s Human Subject Protection Committee. Written, informed consent was obtained from each patient’s parents, and when applicable, from the patient as well.

PROTOCOL

All patients were premedicated with morphine sulfate (MS) 0.1 mg · kg\(^{-1}\) and scopolamine 0.02 mg · kg\(^{-1}\) (maximum dose 0.4 mg) 1 h prior to surgery. Anesthesia was induced with nitrous oxide, oxygen, and halothane by mask. With loss of consciousness, an intravenous infusion was started and a paralyzing dose of \( d \)-tubocurarine (\( d \)TC) (0.6 mg · kg\(^{-1}\)) was given. Halothane was discontinued after oral endotracheal intubation, and anesthesia was maintained with nitrous oxide (70%), oxygen (30%), \( d \)TC (0.2 mg · kg\(^{-1} \cdot h^{-1} \)), MS (initially 0.2 mg · kg\(^{-1}\) and then 0.1 mg · kg\(^{-1}\) every 4 h), and thiopental (1 mg · kg\(^{-1}\) every 30 min). Ventilation was controlled to maintain \( P_a \text{CO}_2 \) between 30 and 35 mmHg as determined by repeated measurements and by use of an end-tidal \( CO_2 \) monitor (Hewlett Packard, Model 2250AO). A radial artery catheter, internal or external jugular central venous catheter, second peripheral catheter, and Foley catheter were placed. In addition, a blood pressure cuff, precordial stethoscope, rectal temperature probe, and ECG were used in all patients. Patients undergoing operations on the spine were monitored with somatosensory-evoked potentials.\(^7\)–\(^10\)
(posterior tibial nerve and common peroneal nerve). Five per cent dextrose in 0.2% saline was infused in a peripheral vein at maintenance rates calculated according to a standard formula. Lactated Ringer’s solution was infused at a rate of 6–8 ml·kg⁻¹·h⁻¹ to replace third-space fluid losses. Estimated blood volumes and allowable blood losses were calculated according to standard formulæ. Blood loss was measured by weighing sponges and measuring the volume of blood in suction bottles. Blood was replaced with 3 ml of lactated Ringer’s solution for each ml of blood lost until the calculated allowable blood loss was reached, at which point lost blood was replaced with an equal volume of transfused blood.

Heart rate (HR), rhythm, arterial blood pressure, central venous pressure (CVP), temperature, and end-tidal CO₂ were monitored continuously and recorded. Cardiac output (CO) was measured using the dye dilution technique. Systemic vascular resistance (SVR) was calculated according to the following formula: SVR = [(mean arterial pressure – CVP)/CO × 80]. Alveolar oxygen tension was calculated according to the standard formula: PAO₂ = [(FₐO₂) (Pₐ – 47) – [Paco₂/0.8]), where Pao₂ is alveolar oxygen tension, Fio₂ represents the fraction of inspired oxygen, Paco₂ is arterial carbon dioxide tension, Pₐ is barometric pressure, and the respiratory quotient is assumed to equal 0.8. The difference between the alveolar and arterial oxygen tensions (A – aDpao₂) was calculated by the formula: A – aDpao₂ = PAO₂ – Paco₂. Base excess (BE) was derived from the measured pH and Paco₂ using the Siggard-Andersen nomogram.

Patients were prospectively randomized by the pharmacy to one of two hypotensive groups: one group (n = 6) received SNP, the other (n = 8) received NTG. All bottles were wrapped in silver foil, and nonpolyvinylchlo- ride administration sets were used to prevent the absorption of NTG into polyvinylchloride tubing. Solutions of both agents were prepared within 30 min of expected use, and concentration was determined by weight such that 1 ml of solution contained either 5 or 10 μg·kg⁻¹. Thus, the anesthesiologist administering the drug, while blinded to the specific agent being used, could administer the drug solution in μg·kg⁻¹·min⁻¹ increments by adjusting the volume delivered.

Infusion of drug was begun at 1.0 μg·kg⁻¹·min⁻¹ and increased in 0.5 μg·kg⁻¹·min⁻¹ increments to decrease mean arterial pressure (MAP) to 55 mmHg or less or to decrease MAP by one-third or more from baseline values. Propranolol was used to maintain HR at less than 110 beats/min. If more than 10 μg·kg⁻¹·min⁻¹ of the test drug was required, the anesthesiologist was unblinded to the agent being used. If NTG was being used, it was continued to the desired effect (i.e., MAP of 55 mmHg or less or a decrease in MAP by one-third or more from baseline values) or until a dose of 40 μg·kg⁻¹·min⁻¹ was reached, at which time the NTG was discontinued and SNP was begun. If the initial drug was SNP and more than 10 μg·kg⁻¹·min⁻¹ was required, SNP was discontinued to avoid cyanide toxicity and NTG was begun. Drug infusion was discontinued, and arterial pressures were allowed to increase before wound closure to secure hemostasis.

CO and arterial blood samples for pH, gas tensions, and hematocrit were obtained 20 min after the patient was positioned in the prone position in those patients undergoing scoliosis surgery or 20 min following the insertion of invasive monitoring in those patients operated on in the supine position. These measurements were also obtained prior to surgery, at the start of surgery, at the initiation of hypotension, at MAP of 55 mmHg or less, or prior to breaking the code (at 10 μg·kg⁻¹·min⁻¹ of drug infusion), at maximum NTG dose, and 20 min after discontinuing the infusion.

**Statistical Methods**

Comparison between NTG and SNP groups (age, weight, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), MAP, CVP, SVR, Pao₂, Paco₂, pH, BE, and A – aDpao₂) were made by unpaired t test. Comparison within the NTG group and SNP group (MAP, SAP, DAP, CVP, cardiac index [CI], SVR, pH, Paco₂, BE, and A – aDpao₂) at baseline, at different drug levels, and following discontinuation of drug infusion was made using one-way analysis of variance with repeated measures. Multiple comparisons were made by the Duncan Multiple Range Test. Probability values of less than 0.05 were considered statistically significant. All data are presented as mean ± SD.

**Results**

There was no difference in age, weight, or control hemodynamic variables or blood gas parameters between the two groups. The average age of the patients receiving NTG was 11.8 ± 3.5 yr, whereas the age of those receiving SNP was 12.6 ± 1 yr. There were six females and two males in the NTG group and four females and two males in the SNP group. Children in the SNP group ranged in weight from 25 to 75 kg (mean 46.4 ± 17.7 kg) and in the NTG group from 21 to 70 kg (mean 42 ± 12 kg).

SNP was successful in achieving an MAP of 55 mmHg or less or a decrease in MAP by one-third or more from baseline values in six out of six children in whom it was the initial drug and in all six children in whom NTG failed. As shown in table 1, SNP significantly decreased SAP, DAP, MAP, and SVR (P < 0.001) and increased CI (P < 0.003) compared with baseline. The dose of SNP required to achieve an MAP of 55 mmHg or less in this study was 6–8 μg·kg⁻¹·min⁻¹. In contrast, NTG de-
TABLE 1. Hemodynamic Values before, during, and after Infusion of Nitroglycerin (NTG) and Sodium Nitroprusside (SNP) (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>SNP</th>
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<th>NTG</th>
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<tbody>
<tr>
<td></td>
<td>MAP</td>
<td>CI</td>
<td>SVR</td>
<td>MAP</td>
</tr>
<tr>
<td>Baseline</td>
<td>82 ± 5</td>
<td>2.37 ± 0.35</td>
<td>1889 ± 499</td>
<td>86 ± 15</td>
</tr>
<tr>
<td>&lt;10 µg·kg⁻¹·min⁻¹</td>
<td>52 ± 2*</td>
<td>4.44 ± 1.36*</td>
<td>676 ± 295*</td>
<td>67 ± 13*</td>
</tr>
<tr>
<td>40 µg·kg⁻¹·min⁻¹</td>
<td>—</td>
<td>—</td>
<td>68 ± 12*</td>
<td>68 ± 12*</td>
</tr>
<tr>
<td>Off drug</td>
<td>96 ± 10*</td>
<td>2.82 ± 1.05*</td>
<td>2158 ± 996</td>
<td>84 ± 13</td>
</tr>
</tbody>
</table>

Mean arterial pressure (MAP) is expressed in mmHg, cardiac index (CI) in l·min⁻¹·m⁻², and systemic vascular resistance (SVR) in dyn·s·cm⁻⁵. * P < 0.05 compared with baseline.

creased DAP and MAP from baseline at 10 µg·kg⁻¹·min⁻¹ and at 40 µg·kg⁻¹·min⁻¹ (P < 0.03); however, it failed to achieve an MAP of 55 mmHg or less or a decrease in MAP by one-third or more from baseline values in six of eight children. NTG produced no significant change in CI; however, SVR decreased significantly from control at both 10 and 40 µg·kg⁻¹·min⁻¹ infusions (P < 0.003). SVR was decreased significantly more in the SNP group at doses of ≤10 µg·kg⁻¹·min⁻¹ than NTG at 10 or 40 µg·kg⁻¹·min⁻¹ (decreases of 64% vs. 29%; P < 0.01).

Following induction of hypotension, HR reflexly increased, and both drug groups required propranolol (range 1–3 mg) to maintain HR at less than 110 beats/min. There was no difference in the amount of propranolol used in either group. Ten minutes following discontinuation of the drug infusion, blood pressure rapidly returned to control or surpassed it in all patients. Those patients receiving SNP had “rebound hypertension,” that is, they had significantly higher blood pressure as compared with control following the discontinuation of SNP.

Compared with baseline, PaO₂ decreased and the A–aD O₂ increased after both SNP- and NTG-induced hypotension; however, the changes following NTG occurred only at the highest infusion rate (table 2). This increase in the alveolar–arterial oxygen gradient persisted following the discontinuation of the drugs. The use of SNP was associated with the development of a mild acidosis in the second hour of infusion (BE of −3 mEq/l). Following several hours of SNP administration pH and BE fell to an average of 7.38 ± 0.01 and −6 ± 1 mEq/l, respectively. At no time was there the development of severe metabolic acidosis (pH < 7.30 or BE > −10 mEq/l) or circulatory instability that we consider signs of cyanide toxicity.

**Discussion**

In this prospective, randomized, double-blind study, NTG at infusion rates as high as 40 µg·kg⁻¹·min⁻¹ was ineffective as an agent to produce rapid, predictable, and sustained decreases in arterial pressure during general anesthesia. Although NTG decreased MAP with increasing dose, it did not decrease MAP below 60 mmHg in six of the eight patients, in whom deliberate hypotension was

TABLE 2. Blood Gas Results before, during, and after Infusion of Sodium Nitroprusside (SNP) and Nitroglycerin (NTG) (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>SNP</th>
<th></th>
<th>NTG</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>MAP</td>
<td>CI</td>
<td>SVR</td>
<td>MAP</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.45</td>
<td>7.42</td>
<td>7.38*</td>
<td>7.41</td>
</tr>
<tr>
<td>&lt;10 µg·kg⁻¹·min⁻¹</td>
<td>0.04</td>
<td>0.05</td>
<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Off Drug</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>pH</td>
<td>31</td>
<td>32</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>BE</td>
<td>−1</td>
<td>−3</td>
<td>−6*</td>
<td>−2</td>
</tr>
<tr>
<td>FIO₂</td>
<td>0.35</td>
<td>0.31</td>
<td>0.32</td>
<td>0.31</td>
</tr>
<tr>
<td>PaO₂</td>
<td>187</td>
<td>148*</td>
<td>132*</td>
<td>160</td>
</tr>
<tr>
<td>PAO₂</td>
<td>216</td>
<td>193</td>
<td>177</td>
<td>175</td>
</tr>
<tr>
<td>A–aD O₂</td>
<td>31</td>
<td>44*</td>
<td>46*</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>13</td>
<td>8</td>
<td>18</td>
</tr>
</tbody>
</table>

PaCO₂, PaO₂, PaO₂, and A–aD O₂ are expressed in mmHg and the base excess (BE) in mEq/l. FIO₂ is the fraction of inspired oxygen and A–aD O₂ is the alveolar–arterial oxygen tension difference. * P < 0.05 compared with baseline.
attempted. There was no clinical advantage in increasing the dose of NTG above 10 μg·kg⁻¹·min⁻¹. On the other hand, SNP produced reliable and rapid hypotension in every patient in whom deliberate hypotension was attempted, including those children in whom NTG failed. The dose required to achieve this effect was 6–8 μg·kg⁻¹·min⁻¹.

These data contrast with those of Fahmy,⁶ who found that NTG effectively lowered blood pressure in adult patients undergoing elective orthopedic surgery at doses ranging between 1.5–7.0 μg·kg⁻¹·min⁻¹ (mean infusion rate of 4.6 μg·kg⁻¹·min⁻¹). This may be explained by differences in the anesthetic technique, the definition of “deliberate hypotension,” and/or patient age. Our study design differed from that of Fahmy in that we conducted a double-blind, randomized study using a different anesthetic technique. We standardized the dose of a balanced anesthetic technique (70% N₂O, 0.3 mg·kg⁻¹ MS, 0.6 mg·kg⁻¹ d TC), whereas Fahmy used halothane (inspired concentrations ranging between 0.5–1.0%). We did not use halothane in this study because of its depressant effects on the somatosensory-activated potential,⁷,⁹,¹⁰ which we routinely use to monitor spinal cord function in spine surgery. Furthermore, the avoidance of halothane allowed us to use the rapid “wake-up test” in those patients in whom evoked-potential amplitudes or latencies changed during surgery.¹⁰,¹⁵ Halothane may significantly potentiate the effect of NTG on blood pressure control because of its myocardial and central nervous system depressant effects. Thus, the absence of halothane may well explain the patients’ resistance to NTG in this study.

We defined “deliberate hypotension” as a lowering of MAP below 55 mmHg or a decrease in MAP by one-third or more from baseline values. Fahmy lowered blood pressure to systolic pressures of approximately 75 mmHg. We used MAP as the determinant of the level of hypotension in this study because it sets the lower limit of autoregulation in most organs, particularly the brain. In the brain this lower limit of autoregulation occurs at MAPs of 50–60 mmHg in normotensive individuals.¹⁶,¹⁷ In the presence of hypertension the lower limit of autoregulation is approximately 70% of MAP.¹⁸ Reducing MAP below 50 mmHg reduces cerebral blood flow and results (in dogs) in decreases in brain energy substrates and increases in glycolytic products.¹⁹ Thus, most reviews suggest an MAP of 50–60 mmHg as the lower limit of blood pressure while using this technique.⁶,⁸ Interestingly, in Fahmy’s paper⁶ the MAP achieved with NTG ranged between 60–63 mmHg, whereas the MAP achieved with SNP ranged between 52–54 mmHg. Therefore, several of the NTG patients considered clinical successes in his study would be considered failures in ours. Finally, age may actively alter the patient’s response to the hypotensive agent. The average age of the patients in Fahmy’s study⁶ was 46 yr; in our study the patients’ average age was 12 yr.

As reported in other studies, both drugs decreased PaO₂ and increased the A – aDO₂.⁶,²⁰,²¹ These changes were small and could easily be treated with small increases in the FIO₂. The most likely cause of this effect is the inhibition of hypoxic pulmonary vasoconstriction by the drugs and a resultant increase in the intrapulmonary shunt (Ql/Qe).²⁰,²¹

Both NTG and SNP are thought to induce hypotension primarily by direct effects on vascular smooth muscle.⁴,²²,²³ SNP affects both resistance and capacitance vessels in a balanced way, whereas NTG is thought to affect primarily the venous capacitance vessels.⁶,²²,²³ How these drugs alter hemodynamics in children has heretofore not been studied. Both drugs decreased SVR, but SNP had a more dramatic effect than NTG on the resistance vessels and thereby caused a more profound decrease in blood pressure. Interestingly, SNP significantly increased CO during the development of hypotension, whereas NTG had no effect. Other investigators have variously reported that CO either increased, decreased, or did not change significantly following SNP.⁴,²⁴,²⁵ Rowe and Henderson,²⁶ using adult dogs, found a 30% increase in CO following an 8% fall in MAP, whereas Kuipers et al.,²⁷ using a 10 μg·kg⁻¹·min⁻¹ infusion of SNP in young lambs, found no change in CO despite a 50% decrease in MAP. Woods and et al.,²⁸ found a significant increase in CO following SNP use in their patients undergoing scoliosis surgery.

The increase in HR seen with both drugs in this study is thought to be a reflex sympathetic nervous system response mediated by catecholamines²⁹ and the renin-angiotensin system.³⁰ Hence, the use of beta-blockers such as propranolol is essential to produce deliberate hypotension in children and adolescents. Both treatment groups in our study required propranolol (range 1–3 mg) to maintain HR at less than 110 beats/min. Following the discontinuance of SNP, significant hypertension occurred. This “rebound hypertension” has been reported by others³¹ and is thought to be secondary to increased plasma renin activity.

Finally, the dose of SNP required to produce an MAP of 55 mmHg or less in this study is at the high end of the suggested dose range,³²,³³ and attention to signs of cyanide toxicity is essential. SNP is metabolized to cyanide via a direct, nonenzymatic reaction with oxyhemoglobin.⁴ The resultant cyanide, if not detoxified, will bind to cytochrome oxidase and produce cellular anoxia by inhibiting aerobic mitochondrial oxidative phosphorylation. Monitoring for cyanide toxicity includes careful attention to dosage, development of a severe metabolic acidosis, and/

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or development of circulatory instability. Our patients did develop a statistically significant, albeit mild, acidosis and base deficit over the course of several hours. At no time, though, was there circulatory instability or excessive acidosis (base deficit in excess of 10 mEq/l or pH less than 7.30) during the drug infusion. During the initial 2 h of drug infusion, BE averaged -3 mEq/l.

In conclusion, intravenous NTG is less effective than SNP for inducing deliberate hypotension in children anesthetized with a balanced anesthetic technique. SNP was uniformly effective in all patients at doses of 6–8 µg·kg⁻¹·min⁻¹ and thereby appears to be the agent of choice for the reliable, sustained, and rapid induction of deliberate hypotension in children and adolescents. Finally, sympathetic blockade is required in children as an adjunct to the balanced anesthetic technique described for the successful induction of deliberate hypotension.

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