

Isoproterenol is an Effective Marker of Intravenous Injection in Laboring Women

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The purpose of this randomized, double-blind study was to determine if isoproterenol 5 μg iv produces a consistent, noticeable tachycardia in healthy, laboring women. Maternal heart rate, fetal heart rate, and uterine contractions were continuously recorded and maternal blood pressure was measured every minute for 10 min before and after each patient received either normal saline (NS group; $n = 10$) or isoproterenol 5 μg (ISO group; $n = 10$) iv. The data-collecting investigator and a nurse palpating the patient's radial artery determined which solution they thought had been administered. The authors analyzed the maternal heart rate tracings using baseline-to-peak (a ≥ 25 beat/min maternal heart rate increase occurring within 120 s of drug injection and lasting ≥ 15 s) and peak-to-peak (a ≥ 10 beat/min increase in the maximum maternal heart rate during the 2-min postinjection over the maximum maternal heart rate during the 2 min preinjection) criteria for detection of an intravascular marker. Mean maternal heart rate in the ISO group was significantly higher than in the NS group 20, 30, 40, 50, and 60 s following the injection ($P < 0.01$). The peak-to-peak criterion and the data-collecting investigator correctly classified all patients. Five ISO group patients were not identified by the baseline-to-peak criterion. The nurse palpating the mother's radial artery misidentified two patients. Systolic blood pressure was significantly higher in ISO group than in NS group patients 1 min ($P < 0.05$) and 2 min ($P < 0.01$) following drug injection. Diastolic and mean blood pressures did not change. No fetal distress occurred. Isoproterenol 5 μg is an effective marker of intravascular injection in laboring women; however, the safety and efficacy of epidural isoproterenol must be demonstrated in animals before isoproterenol can be incorporated in an epidural anesthesia test dose. (Key words: Anesthesia, obstetric. Anesthetic techniques: epidural; obstetric. Sympathetic nervous system: isoproterenol.)

DETECTION OF intravascular placement of epidural catheters is an important yet difficult task in laboring women. Epinephrine 15 μg produces an easily recognized tachycardia when administered intravenously to men and non-pregnant women.¹ However, in unanesthetized laboring women, epinephrine 15 μg iv causes only a brief tachycardia followed by a more prolonged bradycardia.² This tachycardia may escape detection without careful inspection of a recorded tracing of the maternal heart rate.^{2,3} In addition, comparable doses of epinephrine decrease

uterine blood flow in pregnant ewes and guinea pigs.^{4,5} The biphasic heart rate response and concerns about fetal safety make epinephrine 15 μg a poor marker of intravascular injection in laboring women. We postulate that bradycardia occurs reflexly in response to epinephrine-induced hypertension, and that bradycardia would not be seen following the administration of a pure beta-adrenergic agonist such as isoproterenol. We designed this randomized, double-blind study to evaluate the efficacy of isoproterenol 5 μg as a marker of intravascular injection in unanesthetized laboring patients.

Materials and Methods

Twenty unanesthetized, healthy parturients who were between 37 and 42 weeks gestation and carrying single fetuses gave written, informed consent before participating in this study, which was approved by our institutional review board. All patients were laboring (between 3 and 6 cm cervical dilation), were not receiving intravenous oxytocin, and had not received parenteral or epidural medication for pain. Preinjection continuous fetal heart rate tracings appeared normal (fetal heart rate ≥ 120 and ≤ 160 beats/min with long-term variability present, 5–10 beats/min short-term variability and no decelerations). Left uterine displacement was maintained while an HP8040A[®] monitor continuously recorded electrocardiographic maternal heart rate, ultrasonographic fetal heart rate, and tocodynamometric uterine contractions. A Criticon Dinamap 845XT[®] measured maternal blood pressure at 1-min intervals. These measurements were recorded for 10 min before and after each patient randomly received either 5 ml normal saline (NS group; $n = 10$) or isoproterenol 5 μg in 5 ml normal saline (ISO group; $n = 10$) iv 30 s after a uterine contraction. The data-collecting investigator and a labor floor nurse palpating the patient's radial artery, both of whom were unaware of the patient's treatment group, then indicated which solution they thought had been administered.

All determinations of maternal heart rate and evaluations of fetal heart rate patterns were performed by investigators unaware of the solution administered to the patient. We determined maternal heart rate from the maternal heart rate tracings at 10-s intervals for 120 s and at 30-s intervals between 120 s and 240 s after the injection. Each maternal heart rate and mean blood pressure value was expressed as a percentage of that patient's heart rate or blood pressure at the time of the injection (T_0).

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Group values are expressed as the mean \pm standard deviation of the normalized values. An obstetrician (BC) analyzed fetal heart rate tracings for signs of fetal distress (short-term fetal heart rate variability \leq 5 beats/min. more than one late deceleration within 10 min after T_0 , or a change in baseline fetal heart rate to \leq 120 beats/min or \geq 160 beats/min).

We analyzed the maternal heart rate tracings using previously derived baseline-to-peak and peak-to-peak criteria for detection of a marker of intravascular injection.² The baseline-to-peak criterion is a 25 beat/min maternal heart rate increase over the maternal heart rate at the time of drug injection occurring within 120 s of drug injection and lasting \geq 15 s. The peak-to-peak criterion is a 10 beat/min increase in the maximum maternal heart rate during the 2-min postinjection greater than the maximum maternal heart rate during the 2-min preinjection.

Analysis of variance for repeated measures and Duncan's multiple range test determined the significance of postinjection maternal heart rate and blood pressure differences between the groups. Fisher's exact test determined the significance of differences between the groups in the efficacy of the diagnostic criteria. One-way analysis of variance determined the significance of demographic differences between the groups. $P < 0.05$ indicated significance.

Results

Maternal age, height, weight, and gestational age did not differ significantly between the groups. Four patients in each group had a uterine contraction within 60 s of the drug injection.

Maternal heart rate changes are shown in figure 1. Mean maternal heart rate in the ISO group was significantly higher than that of the NS group at all time points between 20 and 60 s following the injection ($P < 0.01$).

Table 1 shows the efficacy of the four diagnostic criteria evaluated in this study. The peak-to-peak criterion and the data-collecting investigator correctly identified the treatment group of all patients. Five ISO group patients were not identified by the baseline-to-peak criterion. The nurse palpating the mother's radial artery misidentified two patients, one from the NS group and one from the ISO group.

Systolic blood pressure was significantly higher in ISO group than in NS group patients 1 min ($P < 0.05$) and 2 min ($P < 0.01$) but not at 3, 4, or 5 min following drug injection (fig. 2). Diastolic and mean blood pressures did not differ between the groups at any time.

No fetal distress was seen in either group, although the fetal heart rate patterns in two patients (one NS group and one ISO group patient) reflected single late decelerations 6-7 min following drug injection.

EFFECT OF ISOPROTERENOL (5mcg) ON MATERNAL HEART RATE

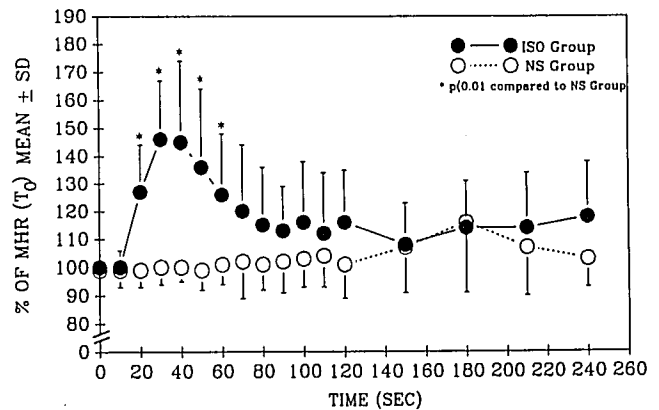


FIG. 1. Maternal heart rate after isoproterenol 5 μ g iv (● — ●) or normal saline (○ - - ○) in unanesthetized laboring patients. We normalized all values for a given patient by expressing them as a percentage of that patient's heart rate at the time of drug injection (MHR (T_0)). Group values are expressed as the mean \pm SD of the normalized values.

Discussion

Intravascular injection of local anesthetics intended for epidural anesthesia can produce serious morbidity or mortality.⁶ Recognized intravascular placement or migration of an epidural catheter occurs in 5.2% of obstetric epidural anesthetics, and detection of these intravascular catheters can be difficult.⁷ Three methods are now recommended to avoid massive intravascular injection of local anesthetic: 1) careful aspiration of the catheter for blood,⁸ 2) injection of a test dose containing epinephrine 15 μ g,⁹⁻¹¹ and 3) fractionation of the local anesthetic dose.⁸ A review of 4,003 obstetric epidural anesthetics found that 33% of the intravascular catheters were not detected by careful aspiration.⁷ Of the intravascular catheters undetected by aspiration, 23% were not identified by fractionated administration of "rather large quantities"

TABLE 1. Efficacy of Diagnostic Criteria

Criterion	Number of Patients Identified as Receiving Isoproterenol	
	NS Group	ISO Group
Peak-to-peak (from MHR tracing)	0/10	10/10
Baseline-to-peak (from MHR tracing)	0/10	5/10
Nurse palpating maternal radial artery	1/10	9/10
Data-collecting investigator inspecting MHR tracing	0/10	10/10

Baseline-to-peak criterion = a maternal heart rate increase of \geq 25 beats/min over the maternal heart rate at the time of drug injection that occurred within 120 s of drug injection and lasted \geq 15 s. Peak-to-peak criterion = a \geq 10 beats/min increase in the maximum maternal heart rate during the 2 min after injection as compared with the maximum maternal heart rate during the 2 min before injection.

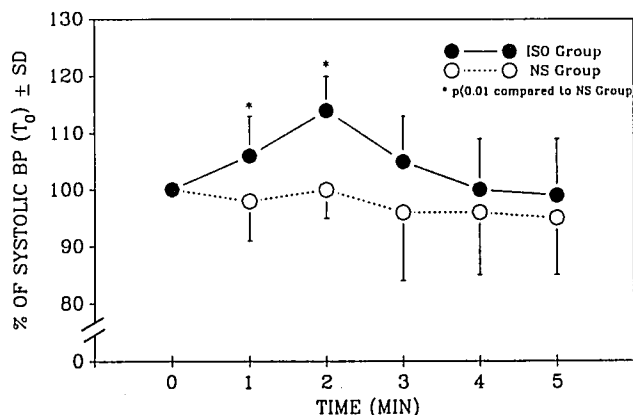
EFFECT OF ISOPROTERENOL (5mcg)
ON MATERNAL SYSTOLIC BLOOD PRESSURE

FIG. 2. Maternal systolic blood pressure after isoproterenol 5 µg iv (●—●) or normal saline (○—○) in unanesthetized laboring patients. We normalized all values for a given patient by expressing them as a percentage of that patient's systolic blood pressure at the time of drug injection (systolic BP (T₀)). Group values are expressed as the mean ± SD of the normalized values.

of local anesthetic.⁷ The injection of a test dose containing epinephrine 15 µg is intended to identify the remaining intravascular catheters.

Accurate diagnosis of intravascular injection using a chronotropic marker is a difficult task in laboring patients. Maternal heart rate varies with uterine contractions by

more than 25 beats/min in 20–50% of unanesthetized actively laboring patients.^{2,3,11} This increased variability makes differentiating a drug effect from natural maternal heart rate variation a difficult task. In addition, because parturients are less responsive than are nonpregnant women to the chronotropic effects of beta-adrenergic agonists, false-negative results may be obtained if one uses a chronotropic marker that is effective in nonpregnant patients but untested in parturients.^{1,2,12} An appropriate chronotropic marker for use in an obstetric epidural anesthesia test dose must, therefore, have demonstrated effectiveness in laboring and nonlaboring parturients.

Epinephrine 15 µg iv produces a transient and difficult to detect tachycardia followed by a more prolonged bradycardia in laboring women.² Careful inspection of recorded maternal heart rate tracings for a ≥10 beat/min increase in the maximum maternal heart rate during the 2 min after the injection compared with the maximum maternal heart rate during the 2 min before the injection correctly identified intravenous epinephrine injection in 9 of ten laboring women (peak-to-peak criterion).² False-negative and false-positive results were obtained when a 25 beat/min increase over baseline in the maternal heart rate was used to indicate epinephrine injection (baseline-to-peak criterion).² In contrast, intravascular injection of epinephrine 15 µg can be easily detected in nonpregnant surgical patients and volunteers by palpating the patient's radial artery or by observing the electrocardiogram.¹

Epinephrine, in doses comparable to 15 µg iv in pregnant women, decreases uterine blood flow in several animal species. In pregnant ewes, epinephrine 10–15 µg with or without local anesthetic decreases uterine blood flow 30–45%, and uterine blood flow remains low for more than 3 min.⁴ Uterine blood flow decreases transiently to 87% of the control value within 1 min following epinephrine 0.2 µg/kg iv in pregnant guinea pigs.⁵ Although the percent decrease in uterine blood flow following epinephrine is not greater than the decrease seen in pregnant sheep and dogs following a normal uterine contraction,¹³ the epinephrine studies were conducted in healthy, nonlaboring animals with undistressed fetuses.^{4,5} It is not known if intravenous epinephrine and uterine contractions have cumulative effects on uterine blood flow. An intravascular marker that did not decrease uterine blood flow would provide a greater fetal safety margin.

Isoproterenol possesses several theoretical advantages over epinephrine as a chronotropic marker of intravascular injection. Isoproterenol has nearly exclusive beta-adrenergic agonist activity, so a biphasic heart rate effect or bradycardia should not occur.¹⁴ Isoproterenol may also have a larger fetal safety margin than epinephrine. In pregnant guinea pigs, placental blood flow did not decrease during infusion of isoproterenol 0.05 µg·min⁻¹·kg⁻¹, a dose sufficient to increase the maternal heart rate 40 beats/min.¹⁵

TWO CRITERIA FOR ISOPROTERENOL INJECTION

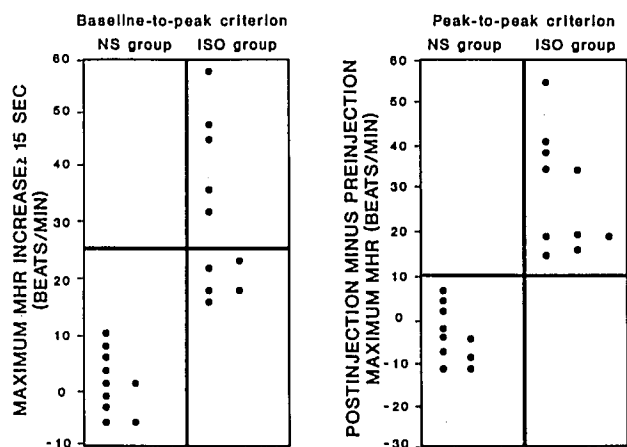


FIG. 3. Analysis of the maternal heart rate changes following intravenous administration of isoproterenol 5 µg or normal saline to unanesthetized laboring patients according to two previously derived criteria for detection of a chronotropic intravascular marker. Baseline-to-peak criterion: a ≥25 beat/min maternal heart rate increase over the maternal heart rate at the time of drug injection occurring within 120 s of drug injection and lasting ≥15 s. Peak-to-peak criterion: a ≥10 beat/min increase in the maximum maternal heart rate during the 2-min postinjection over the maximum maternal heart rate during the 2-min preinjection.

We chose the dose of isoproterenol used in this study, 5 μg , after conducting an isoproterenol dose-response study in healthy term-pregnant women. The mean dose of isoproterenol needed to raise the heart rate 25 beats/min (CD25) in term-pregnant women is 3.6 μg .¹² We used an isoproterenol dose slightly higher than the CD25 for term-pregnant women in order to produce a noticeable tachycardia in all patients receiving isoproterenol.

Although isoproterenol is a vasodilator, systolic blood pressure was slightly higher in the isoproterenol than in the saline group at 1 and 2 min following injection. Mean and diastolic blood pressures did not differ. We postulate that isoproterenol-induced increases in myocardial contractility and cardiac output compensated for any vasodilating effects, resulting in a small net increase in systolic blood pressure.

The present study re-emphasizes the necessity of carefully examining maternal heart rate changes before and after injection of a chronotropic marker to accurately detect intravascular injection in laboring women. We were able to correctly identify the treatment group of all patients by applying the peak-to-peak criterion to continuous maternal heart rate tracings. However, five patients who received isoproterenol were not identified when the baseline-to-peak criterion was applied to these maternal heart rate tracings. Two patients were misidentified by the nurse palpating the radial artery. While larger doses of a beta-adrenergic agonist might produce a more easily detected tachycardia, we question the safety of this approach as isoproterenol 5 μg (fig. 3) and epinephrine 15 μg^2 can cause a very pronounced tachycardia in some parturients.

Further research in several areas must be done before isoproterenol could be incorporated into an epidural anesthesia test dose. First, it is not known if the efficacy of isoproterenol as an intravascular marker changes when it is combined with local anesthetics. Second, the effect of isoproterenol on the quality and duration of concurrently and subsequently administered local anesthetic is unknown. Finally, the safety of intrathecal or epidural isoproterenol has not yet been established in animal studies.

In summary, we found that isoproterenol 5 μg produced a maternal tachycardia that was easily detected using the peak-to-peak criterion for intravascular injection. Maternal systolic blood pressure increased slightly 1 and 2 min following isoproterenol injection, while the mean and diastolic blood pressures and fetal heart rate patterns did not change. Isoproterenol 5 μg is an effective marker

of intravascular injection in laboring women; however, the safety and utility of intrathecal and epidural isoproterenol must be determined in animals before isoproterenol can be incorporated in an epidural anesthesia test dose.

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