

Embolic Activity Subsequent to Injection of the Internal Mammary Artery with Papaverine Hydrochloride

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ABSTRACT

Background: Neurologic injury is a rare yet devastating outcome of coronary artery bypass grafting surgery. Mechanisms producing both focal and global neurologic injuries include embolization, cerebral hypoperfusion, and hypotension. In this present study, we report an association between variations in the treatment of the internal mammary artery with the detection of cerebral embolic signals.

Methods: An intensive intraoperative neurologic and physiologic monitoring approach was implemented to associate discrete processes of clinical care with the concurrent detection of cerebral embolic signals, cerebral hypoperfusion, and hypotension. The method of treating the left internal mammary artery was tracked among 68 patients undergoing isolated coronary artery bypass grafting. Cerebral embolic signals were counted within 3 minutes of the treatment of the left internal mammary artery.

Results: Among a series of 68 patients undergoing isolated coronary artery bypass grafting, 22 were not treated with papaverine. Of those treated, 12 received injection intraluminally and 28 had a topical application. Embolic signals were noted concurrently among 7 patients receiving injection of papaverine. No embolic signals were noted among patients who were treated topically.

Conclusions: We report an association between the injection of papaverine hydrochloride and cerebral embolic signals. Our findings suggest that adoption of topical applications of papaverine hydrochloride may offer opportunities to reduce a portion of cerebral embolic signals in the setting of coronary artery bypass grafting.

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INTRODUCTION

The internal mammary artery (IMA) has long been used as a conduit for CABG procedures, due in part to its association with long- and short-term patency and survival [Leavitt 2001]. During the operative procedure, surgeons often treat the IMA with solutions of papaverine hydrochloride to vasodilate or prevent vasospasm of the artery. The method of action for papaverine has been widely studied, and variation in its application has been previously noted [Girard 2004]. Papaverine's usefulness derives from its spasmolytic effects on smooth muscle and its ability to improve blood flow at the time of the anastomosis.

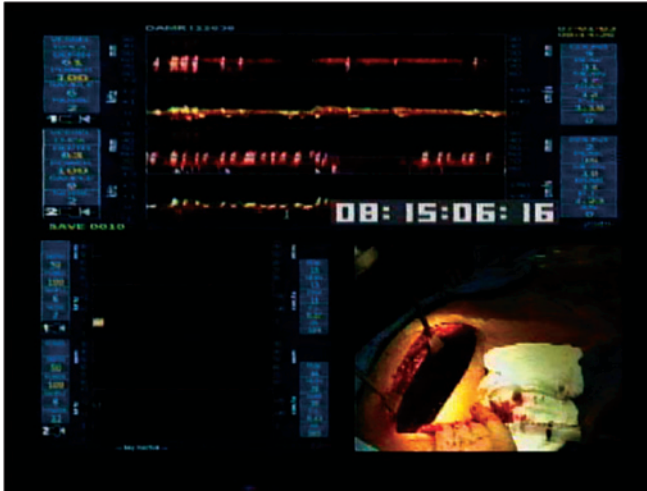
Previous work has implicated embolization as the predominant mechanism producing neurologic injury after CABG surgery [Likosky 2003]. We have previously described a model for identifying the association between discrete processes of clinical care and the creation of precursors of neurologic injury (embolism, hypotension, and cerebral hypoperfusion) among patients undergoing cardiac surgery [Likosky 2004]. In the current study, we identified the association between variations in the treatment of the left internal mammary artery using papaverine hydrochloride with the detection of embolic signals in the cerebral arteries.

MATERIALS AND METHODS

The study protocol received approval by the participating institution's internal review board, and informed consent was received from all study patients.

We performed a prospective cohort study at a single institution in northern New England. We adopted an intraoperative neurologic monitoring model that involves synchronizing the detection of cerebral embolic signals in a patient's right and left cerebral arteries, using power M mode transcranial Doppler monitoring (Spencer Technologies, Seattle, WA, USA), with the videotaping of the surgical field. We used the Doppler device's automatic embolic detection algorithm to count the number of embolic signals subsequent to the treatment of the left internal mammary artery (LIMA) with a solution of 2 mg/mL papaverine hydrochloride ($C_{20}H_{21}NO_4 \cdot HCl$).

All analyses were performed using the STATA 8.0 program (Stata Corporation, College Station, TX, USA). Comparisons



Injection of papaverine hydrochloride into the left internal mammary artery. The bottom right quadrant depicts the injection of papaverine hydrochloride into the left internal mammary artery. The top right and left quadrants depict emboli and blood flow velocity in the right (top two bands) and left (bottom two bands) middle cerebral arteries. An embolus shows up in both bands because the embolus reflects ultrasound more strongly than the surrounding blood. The bottom left quadrant depicts emboli and blood flow velocity through the cardiopulmonary bypass circuit. (No emboli are noted because cardiopulmonary bypass has not been initiated.)

of detected embolic signals by method of LIMA treatment were assessed using χ^2 tests with the Fisher exact test.

RESULTS

Among a series of 68 patients undergoing cardiac surgery, 22 were not treated with papaverine. Information was incomplete on 6 patients (both embolization data or method of treatment). Of the 40 patients treated with papaverine hydrochloride, 12 received injection intraluminally and 28 had topical application. Total embolic signals varied by method, $p_{\text{exact}} < 0.001$. Embolic signals (mean 23, standard deviation 65) were noted concurrently among 12 patients receiving injection of papaverine (Figure, Table). No other surgical processes occurred during the time period of the injection of papaverine. Embolic signals were not observed when alternative treatment, topical application of the LIMA with papaverine, was used. None of the patients in the current study developed a focal neurologic deficit or died within the index admission.

DISCUSSION

We identified embolic signals in the cerebral arteries with the injection, but not the topical application, of papaverine hydrochloride into the LIMA. The range of embolic signals is variable and smaller in magnitude than that seen with other surgical processes of care, such as the onset of cardiopulmonary bypass [Willcox 1999]. However, the occurrence of these embolic signals appears preventable with the adoption

Range of Cerebral Embolic Signals Subsequent to Injection of the Internal Mammary Artery with Papaverine Hydrochloride

Patient	Cerebral Embolic Signals
1	0
2	0
3	0
4	0
5	0
6	1
7	1
8	3
9	3
10	10
11	30
12	228

of alternative strategies, such as not treating the IMA or topically applying the solution. It is not clear whether the embolic signals noted on the transcranial Doppler reflect air entrained within the syringe or particulates. Papaverine is acidic, and its use could result in denaturing of proteins.

Mathis described the association between varying concentrations of papaverine hydrochloride and the likelihood of the formation of precipitates when mixed with human blood [Mathis 1994]. Mathis found that concentrations of $> 0.3\%$, when mixed with human blood, formed crystals between 50-100 microns. Precipitates were returned to solution with the addition of additional sera. Muth reported that emboli, both solid and gaseous, result in damage to cerebrovascular endothelium as well as the production of global and focal neurologic deficits [Muth 2000]. While none of the patients receiving intra-arterial papaverine hydrochloride solution developed a focal neurologic deficit, our findings would suggest that topical application of papaverine hydrochloride should be considered as a viable alternative.

Potential sources of these embolic signals include air (from the syringe) or particulates (secondary to either denaturing of blood formed elements or formation of crystals out of the solution). Regardless of the type of embolic signal, our findings suggest the need for a closer examination of the method for preparing the internal mammary artery.

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