Prevention of Lidocaine-Infusion Phlebitis by Heparin and Hydrocortisone*

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Previous reports have suggested that infusions of lidocaine (lignocaine) cause a high incidence of phlebitis. We investigated the possibility of reducing this high incidence by the addition of small amounts of heparin or hydrocortisone (or both) to the infusate of lidocaine. One hundred patients with acute myocardial infarction who were to receive a 48-hour prophylactic infusion of lidocaine (2.25 mg/min) were randomized to have one of the following added to their infusate in double-blind fashion: (1) placebo; (2) heparin (4,000 units/24 hr); (3) hydrocortisone (20 mg/24 hr); or (4) heparin and hydrocortisone. After 48 hours the incidence of phlebitis was 94 percent in the control group but only 41 percent in the group receiving heparin and hydrocortisone ($p < 0.005$). Had the infusion been stopped after 24 hours, the incidence of phlebitis would have been 56 percent in the group receiving placebo, but only 19 percent in the drug-treated groups ($p < 0.01$). We conclude that infusion of lidocaine causes a high incidence of phlebitis which can be markedly reduced by adding heparin or hydrocortisone (or both) to the infusate and limiting the duration of the infusion in a given vein to 24 hours.

The prophylactic administration of lidocaine (lignocaine) by infusion for the first 48 hours after an acute myocardial infarction has been shown to be effective in preventing primary ventricular fibrillation.[1,2] Based upon these studies[1,2] and the recommendations of others,[3,4] it has been our practice to administer lidocaine to all patients with acute myocardial infarction. We have been struck by the high incidence of phlebitis associated with the infusion of lidocaine, a finding reported by others.[5,6] We reviewed the literature regarding methods of preventing infusion-induced phlebitis, and the most promising seemed to be the addition of heparin[5,7-9] or hydrocortisone[6,7,10,11] to the infusate. We, therefore, carried out a prospective, randomized double-blind trial to see whether small doses of heparin or hydrocortisone (or both) added to the infusion would be effective in reducing the incidence of lidocaine-induced phlebitis.

Materials and Methods

One hundred patients with definite or probable acute myocardial infarction, who were to receive a 48-hour prophylactic infusion of lidocaine, were randomly assigned to have one of the following added to their infusate: (1) saline placebo; (2) heparin (4,000 units/24 hr); (3) hydrocortisone (20 mg/24 hr); or (4) heparin (4,000 units) plus hydrocortisone (20 mg/24 hr). Two coded vials were prepared for each patient by the hospital's pharmacy, with each vial containing either heparin, hydrocortisone, or physiologic saline solution. The lidocaine was administered directly into the vein through a short plastic cannula as a 1.5 percent solution via a constant-infusion pump (Harvard) at 2.25 mg/min, and 0.5 ml from each vial was added to each new syringe of lidocaine every six hours. The two-vial system with the addition of drugs to the lidocaine immediately prior to use was designed to prevent the effects of possible interactions among the drugs or changes in pH following prolonged contact, since the various combinations are known to be unaffected by contact with each other for at least eight hours.[12] The site of infusion was observed at least every eight hours by the nursing staff, and the presence or absence of phlebitis was recorded. Tenderness and redness at the site were necessary for establishing the diagnosis of phlebitis.

Thirty-one patients were excluded from analysis after randomization, for the following reasons: (1) infusion stopped prior to 48 hours (*eg*, due to infiltration, toxicity, death, etc) without signs of phlebitis (23 patients); (2) patient received full-dose intravenous therapy with heparin (four patients); or (3) technical problems in administration or recording (four patients). All exclusions, as well as the determination as to whether and when phlebitis had occurred, were made prior to opening the code. The study was approved by the hospital's committee on research involving human subjects.

Evaluation of the statistical significance of the differences in the incidence of phlebitis among the four treated groups was performed by means of an analysis of heterogeneity using a simultaneous testing procedure.[13] The χ^2 test for marginal homogeneity[14] was used to compare the difference in the incidence of phlebitis at 24 hours of infusion from that at 48 hours.

Results

The numbers of patients in each of the four treated groups who developed phlebitis or were free of it after the 48-hour infusion of lidocaine are listed in Table 1. Almost 95 percent of the patients who received lidocaine alone developed phlebitis. The group which received heparin plus hydrocortisone had a reduction in the incidence of phlebitis of about 50 percent

Table 1—*Incidence of Phlebitis after 48 Hours of Infusion of Lidocaine*

Group	No Phlebitis	Phlebitis
Placebo	1	17
Heparin	5	11
Hydrocortisone	5	13
Heparin and hydrocortisone	10	7*

*$p < 0.005$ vs placebo.

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Table 2—*Incidence of Phlebitis after 24 Hours of Infusion of Lidocaine*

Group	No Phlebitis	Phlebitis
Placebo	8	10
Heparin	18	3*
Hydrocortisone	13	5*
Heparin and hydrocortisone	15	3*

*$p<0.01$ vs placebo.

compared to the group receiving placebo ($p<0.005$). There was no statistically significant difference between either of the other two groups receiving a drug and the group receiving placebo.

We examined the data to see what would have been the incidence of phlebitis in the different groups had the infusion been stopped after 24 hours. There were seven patients in whom the signs of phlebitis appeared between 25 and 28 hours, and we assumed that these seven patients (four with placebo, one with heparin, and two with hydrocortisone) would have developed phlebitis even if the infusion would have been stopped at 24 hours. Table 2 lists the incidence of phlebitis as if the infusion had been stopped after 24 hours. It includes six of the 23 patients who did not develop phlebitis but were excluded from Table 1 because their infusion did not run for 48 hours, but whose infusion did run for at least 24 hours. All three groups receiving a drug had significantly less phlebitis than the control group ($p<0.01$). The incidence of phlebitis for the total cohort was significantly less after 24 hours of infusion than after 48 hours (28 percent vs 70 percent; $p<0.005$).

The sites of infusion were hand, wrist, and antecubital fossa, with no difference among them regarding the incidence of phlebitis.

Discussion

Our control group, which received plain lidocaine, developed a very high incidence of phlebitis of 94 percent at 48 hours and 56 percent after a 24-hour infusion. We did not have a control group receiving glucose or saline solution to compare with this group; however, other investigations in which short plastic catheters were also used have found rates of phlebitis after two days of infusion of glucose solutions of 8 percent,[6] 20 percent,[9] and 22 percent,[13] or, after 24 hours of infusion, rates of 1 percent,[6] 6 percent,[5] and 7 percent.[9] Thus the incidence of phlebitis associated with an infusion of lidocaine was clearly much higher than what might be expected from an infusion of glucose or physiologic saline solution. Similar to our results, Nordel et al[5] found a 52 percent incidence of phlebitis after 24 hours of a 2-mg/min infusion of lidocaine (vs 6 percent in their glucose control group). Likewise, Sketch et al[6] found a 30 percent incidence of phlebitis after an infusion of lidocaine (duration not stated), compared to 15 percent in the control group.

It might be suspected that our practice of giving a 1.5 percent solution of lidocaine directly into the vein could be responsible for the high incidence of phlebitis we observed; however, Nordel et al[5] found the same incidence of phlebitis using a similar dosage of lidocaine diluted in 1,000 ml of a 5 percent glucose solution over 24 hours.

We found that heparin, hydrocortisone, or their combination markedly reduced the incidence of phlebitis after a 24-hour infusion, whereas only the combination of heparin plus hydrocortisone was effective for 48 hours.

In attempting to determine what the incidence of phlebitis would have been had the infusion been stopped after 24 hours, our adding the cases of phlebitis developing only over the subsequent four hours was somewhat arbitrary. Nevertheless, extending the period by 6 to 30 hours (two more patients, one with placebo and one with heparin) or by 12 hours to 36 hours (five additional patients, one with placebo, one with heparin, and three with hydrocortisone) would not have altered the conclusions regarding the effectiveness of the added drugs to 24 hours.

The duration of infusion had an important effect on the incidence of phlebitis. The incidence of phlebitis was more than doubled (from 30 percent to 70 percent) between 24 and 48 hours.

Our data would suggest that by taking advantage of two factors (*ie*, the addition of heparin or hydrocortisone (or both) and the reduction of the time of infusion), the incidence of lidocaine-induced phlebitis following a 48-hour infusion could be reduced from over 90 percent to less than 20 percent. In practice, this would mean adding 4,000 units of heparin and 20 mg of hydrocortisone to each day's volume of lidocaine infusate and changing the site of infusion after 24 hours.

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