Indium-111-Labeled Human Platelets: Improved Method, Efficacy, and Evaluation

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An improved method for labeling human platelets with In-111 oxine is described. The method used modified Tyrode's solution (MTS) as a labeling medium and allowed 86 ± 7% incorporation of In-111 into platelets, which upon stimulation with ADP aggregated 66 ± 15% of control platelets. This compared favorably with the 5% radioactivity uptake in plasma and the 36 and 55% aggregability of platelets labeled in saline and citrated saline, respectively. The influence of parameters affecting the platelet aggregability were examined. The studies revealed that excess of oxine (50 μg oxine/1.6 × 10^9 platelets in 1 ml MTS), and centrifugation at greater than 1000 *g*, reduced platelet aggregability. Excess of oxine also caused a dose-dependent release of In-111 from platelets labeled either in MTS or in plasma, but 4 millimol EDTA did not. Release of In-111 upon aggregation of platelets labeled in either medium was negligible.

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Since the initial report by Thakur et al. (*1*) dealing with the preparation of indium-111 8-hydroxyquinoline (In-111-oxine) platelets and their preliminary evaluation for the in vivo detection of experimental lesions, In-111-platelet scintigraphy has become an acceptable technique for the detection of a variety of vascular lesions induced in laboratory animals (*1–8*). Since the plasma transferrin prevented an efficient incorporation of In-111 activity into platelets, the labeling of the animal platelets in the above investigations had been performed by washing and suspending platelets in normal saline. We have observed that human platelets labeled in normal saline aggregated poorly and cleared from blood circulation rapidly, and this has been further substantiated by Goodwin et al. (*9*). Methods for labeling human platelets in citrated plasma (*10*) and citrated saline (*11*) have been reported. However, the amount of In-111 radioactivity incorporated into platelets suspended in citrated plasma is much lower than with suspension in citrated saline, a medium that permits much lower aggregability than the plasma medium. Davis et al. (*12*, Michael Welch, private communication) have used Tyrode's solution as a labeling medium but have since reported that the medium allowed variable labeling yields (*13*). Hawker et al. (*14*) have observed that Tyrode's solution permitted an efficient incorporation of In-111 into human platelets, but their medium also contained prostaglandin E-1 and heparin, known to induce aggregation of washed platelets (*15*).

This article describes an improved method that uses modified Tyrode's solution (MTS), as a labeling medium, allows an efficient incorporation of In-111, and preserves platelet aggregability and ultrastructure. The article also discusses the evaluation of various parameters that may modulate platelet reactivity and adversely affect platelet aggregability.

MATERIALS

Reagents. The MTS and anticoagulants A and B were prepared as given below, filtered through a 0.22-μ Millipore filter, and refrigerated in 10-ml sterile glass vials.

MTS. A 250-ml MTS solution was prepared (*12*) by dissolving in double-distilled water 3.8 g of NaOH, 6.7 g of monohydrated citric acid ($H_3C_6H_5O_7 \cdot 1H_2O$), 40 g NaCl, 1 g KCl, 2.16 g $MgCl_2 \cdot 6H_2O$, and 5 g glucose. One milliliter of this solution was drawn into a sterile syringe, diluted to 20 ml with sterile water, and heated to 37°C before use (pH = 6.5). The stock solution was prepared once every 3 mo.

Anticoagulants A and B. Anticoagulant A (pH 4.5) was prepared by dissolving in 200 ml double-distilled water, 5 g of dihydrated trisodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$) and 2.98 g of monohydrated citric acid. When 6 ml of this solution was mixed with 34 ml blood, the pH dropped to ~6.5 (*16*).

Isotonic (3.8%) trisodium citrate solution used as anticoagulant B was also prepared and stored as above. When 1.5 ml of this solution was mixed with 15 ml of blood, the plasma pH was ~7.4 (*16*).

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METHODS

Platelet separation and labeling procedure. Thirty-four milliliters of venous blood were drawn from healthy human volunteers into a sterile, disposable plastic syringe containing 6 ml of anticoagulant A. Using the same needle, a further 15 ml of blood were drawn also into a sterile syringe containing 1.5 ml of anticoagulant B. In a laminar flowhood, the blood with anticoagulant A was gently transferred in equal volumes into two 50-ml sterile, conical plastic tubes,* and the blood with anticoagulant B into a third test tube. These were then centrifuged at 180 *g* for 15 min in a calibrated, horizontal swing-rotor table-top centrifuge.

The platelet-rich plasma (PRP) A from both test tubes was isolated and combined. The PRP B was isolated similarly. Care was taken to remove a maximum volume of plasma but to avoid contamination with red cells. A 0.5-ml aliquot of PRP B was separated and stored (22°C) as a reference for subsequent aggregation studies. The PRPs A and B were then centrifuged at 1000 *g* for 10 min, and the platelet-poor plasmas (PPPs) from A and B were separated and stored separately at 37°C. The traces of plasma in the platelet button A were eliminated by layering and removing, twice, 2 ml of MTS at 37°C. Platelets were then suspended in 4 ml MTS (37°C), and a required volume of commercially obtained In-111 oxine† was withdrawn from the vial, diluted fourfold with MTS, and added dropwise to the platelet suspension. The platelets were then incubated at 37°C for 10 min, and 4 ml of PPP A were added. The mixture was centrifuged at 1000 *g* for 10 min, and radioactivity associated with platelets and supernate was measured in a dose calibrator.

The labeled platelets were finally suspended in 5 ml PPP B, incubated at 37°C for 15 min, and a 0.5-ml aliquot was withdrawn for platelet count and aggregation studies. The remainder of the platelets can be used for intravenous administration.

Comparison of In-111 uptake and aggregation of platelets labeled in different media. The object of this study was to compare the efficacy of the plasma, MTS, and saline media for the In-111 uptake of the platelets and their subsequent aggregability. Platelets for the PPP A and saline media were prepared following the methods of Scheffel et al. (*10*) and Thakur et al. (*1*), respectively. Platelets for the MTS medium were prepared as described above. These were suspended in 6 ml of the medium of interest, platelet counts were determined, and 1-ml aliquots were dispensed in test tubes.*

Approximately 10 μl of In-111 oxine, diluted to 40 μl with 0.9% NaCl, were added to each test tube and incubated at 37°C. The test tubes were withdrawn one at a time at predetermined intervals, and equal volume of PPP A was added, and the mixture centrifuged for the determination of labeling efficiency. Platelets in each pellet were finally suspended in 1 ml PPP B, incubated at 37°C for 15 min, and the aggregability of the labeled and the unlabeled reference platelets was measured. Platelets were also labeled by the method of Heaton et al. (*11*) for aggregation studies. For each medium the experiment was performed three times. The aggregation was induced with adenosine diphosphate (ADP, 20 μM) and measured with an aggregometer‡ coupled to a chart recorder.

Influence of oxine; ethanol and radioactivity. This study was designed to evaluate the influence of oxine, ethanol, and radioactivity on the aggregation of human platelets labeled in MTS. The platelets were suspended in a known volume of MTS, their concentration was determined, and 1-ml aliquots were dispensed each into several test tubes. No reagents were added to the platelets in the first test tube, which served as a control. To the remainder of the test tubes, ethanol, oxine, and the In-111 oxine were added in such a way that the concentration of the component under investigation increased progressively while the concentrations of the other two components remained constant. This was achieved by using oxine and In-111 oxine stock solutions of different concentrations and adding ethanol as required. The platelets were then subjected to the MTS labeling procedure and a 0.45-ml aliquot was used for aggregation studies.

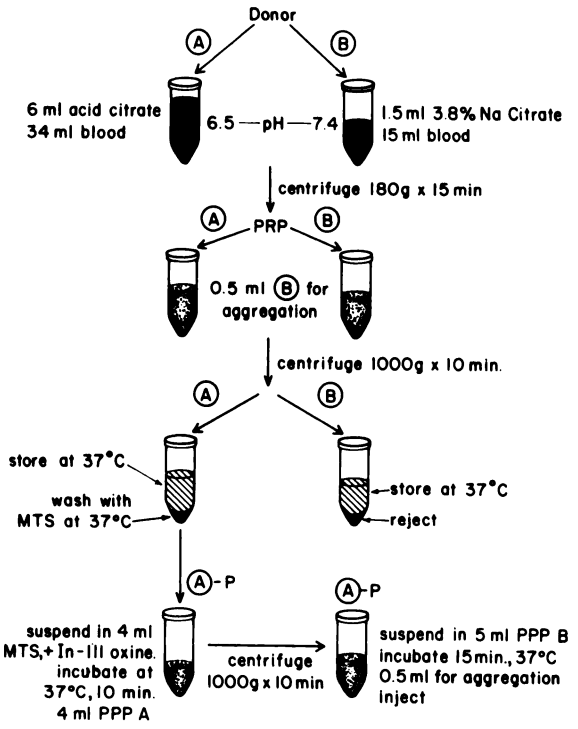

FIG. 1. Schematic presentation of procedure for labeling human platelets with In-111 oxine (for clarification see Methods).

Influence of centrifugal force. Platelets were isolated as described in "platelet separation and labeling procedure," washed with PPP B, and suspended in PPP B to obtain approximately 1.9×10^9 platelets per milliliter. The suspension was then divided into several 1-ml portions and incubated at 37°C for 15 min. These (except those in the control test tubes) were then centrifuged for 10 min at different predetermined centrifugal forces, resuspended in 1 ml PPP B, and their aggregability was determined.

Influence of oxine and EDTA on In-111 release from labeled platelets. Human platelets labeled in MTS or plasma were washed free of radioactivity and suspended in 6 ml of either MTS or PPP B. To five 1-ml portions of these suspensions were added 5–200 μg of oxine in 10 μl ethanol. The sixth portion received 10 μl of ethanol alone. Platelets in the other set of test tubes prepared similarly, received 10 μl of 0.4 *M* EDTA solution. The platelets were then incubated at room temperature for 15 min, centrifuged, and the radioactivities associated with platelets and released in the suspending medium were measured.

Electron microscopy. The control and MTS labeled platelets were subjected to electron microscopy examination using the procedure described previously (*17*).

RESULTS

The improved procedure for labeling human platelets with In-111 is illustrated schematically in Fig. 1. The use of MTS stock solution stored for more than 3 mo, and washing of platelets only once with MTS, resulted in reduced labeling efficiency. When MTS was layered and removed twice, the labeling efficiency was consistently higher, averaging (86 ± 7)% after 10 min of incubation at 37°C.

Figure 2 indicates that platelets suspended in plasma achieve

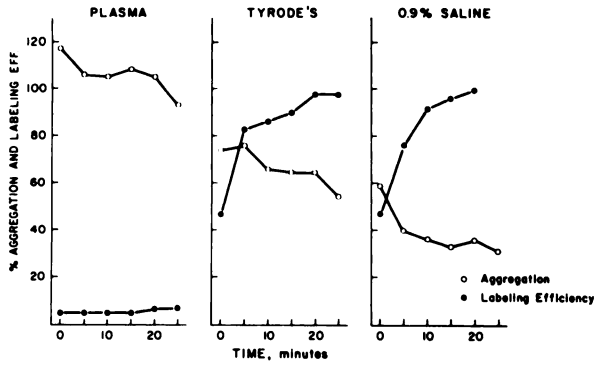

FIG. 2. Influence of suspending medium on labeling efficiency and aggregabiliy of In-111-labeled human platelets (percentages are mean values of three experiments).

much lower labeling efficiency than those suspended either in MTS or in 0.9% NaCl. This renders the plasma medium unacceptable in spite of the high aggregability it permits. The prolonged incubation time in each medium affected the platelet reactivity adversely as manifested by the reduced aggregability. However, at a 10-min incubation period the MTS medium permitted much higher platelet aggregability (66 ± 15%, N = 20) than did either 0.9% NaCl (36 ± 8%) or citrated NaCl (55%, not shown in the figure). Electron microscopy revealed that the labeling procedure did not induce any marked change in the ultrastructure of labeled platelets.

In light of the data (mean values) given in Figs. 3A, B, and C, the reduction in aggregation of labeled platelets could not be attributed to the addition of either the oxine, ethanol, or radioactivity used in the normal preparation (platelets 10^9/ml, ethanol 5 μl/ml, oxine 5 μg/ml, and In-111 100 μCi/ml). This held true even when the radioactivity, ethanol, and oxine concentrations were raised by factors of 2.5, 3, and 4, respectively. However, the platelet aggregability was further reduced to some extent ($p < 0.25$) when 1.6×10^9 platelets were exposed to 50 μg oxine.

The influence of centrifugal force on platelet aggregability demonstrated in Fig. 4 (means of three tests) clearly indicates the injurious effects of higher centrifugal force. When platelets were centrifuged at 1800 *g* for 10 min, their aggregability was significantly reduced ($p < 0.005$).

The release of In-111 radioactivity from labeled platelets exposed to oxine was dramatic in both plasma and MTS. Labeled platelets exposed to 10 μg oxine for 15 min at room temperature released 57.8% (54.2–64.2%) of their In-111 in plasma and 48.3% (42.1–54.4%) in MTS. The release increased gradually with increasing amounts of oxine, and reached 84.1% (79.8–88.4%) and 79.6%, respectively, at 200 μg oxine. This is consistent with the observations made by Scheffel et al. (*10*). On the other hand, as observed previously (*14*), labeled platelets suspended in either MTS or plasma and exposed to 4 millimole EDTA for 15 min at room temperature (N = 4), released only 1.1% (0.9–1.2%) and 2.2% (0.8–3.6%) of incorporated radioactivity. Upon aggregation (N = 4) the release of In-111 activity from these platelets was only 2.8% (1.6–3.6%) and 2% (1.2–2.5%), respectively.

DISCUSSION

It has been observed that canine, rabbit, and baboon platelets labeled in 0.9% NaCl preserved their physiologic function satisfactorily whereas human platelets labeled similarly did not. This has impeded to some extent the use of In-111-labeled platelets in humans. Labeling platelets in citrated plasma has the virtue of higher platelet aggregability (Fig. 2). However, its poor labeling efficiency in our laboratory made the method unacceptable. Lower labeling yields in citrated plasma have also been reported for canine and rabbit platelets (*9,18,19*). The MTS method, as described here, is derived from previously reported methods (*1,12,14,16*) and allows an efficient incorporation of radioactivity [(86 ± 7)%] and satisfactory platelet aggregability [(66 ± 15)%]. This compared favorably with the 5% (4–6%) radioactivity uptake by platelets suspended in plasma and 36 ± 8% and 55% aggregability of platelets labeled in saline and citrated saline, respectively. The method also preserves the platelet ultrastructure and eliminates the use of heparin and prostaglandin E.1.

However, there are many parameters in the labeling procedure that may potentially alter the platelet reactivity. These were studied by aggregation, a commonly accepted photometric test that provides an insight into platelet physiology. Oxine may cause deleterious effects by introducing into platelets toxic elements, such as Cd^{2+}, that may be found in the In-111 solution or by depriving the platelets of certain essential metal ions such as Ca^{2+}. At the level of normal oxine concentration (5 μg for 10^9 platelets in 1 ml) the platelet response appeared normal, but it certainly was impaired when platelets were exposed to ten times this concentration. This concurs with previous observations (*1*). While the exact mechanism by which oxine damages the cell is unknown, the fact

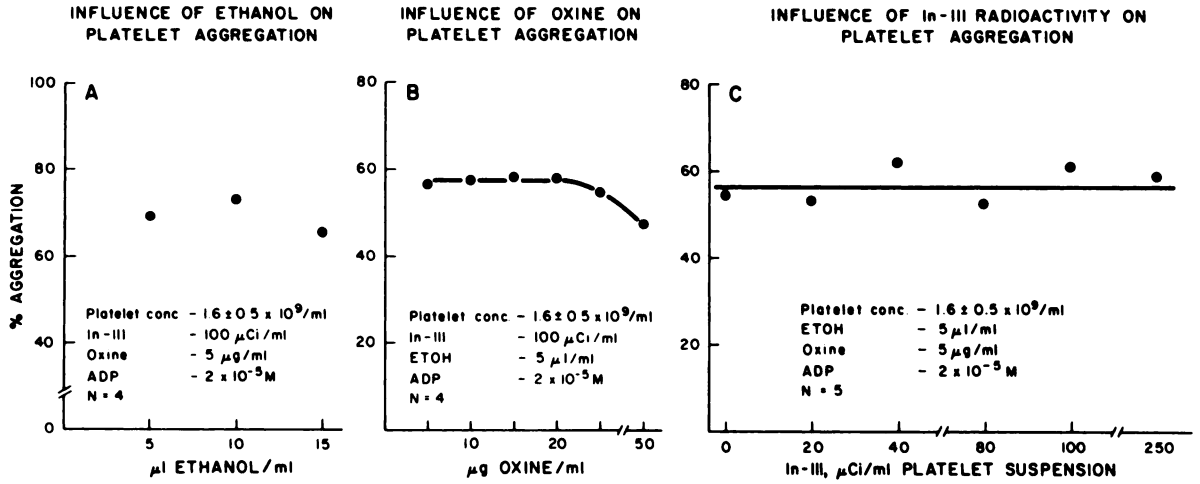

FIG. 3. Influence of ethanol (A), oxine (B), and radioactivity (C) on aggregation of human platelets labeled in modified Tyrode's solution (see text for clarification).

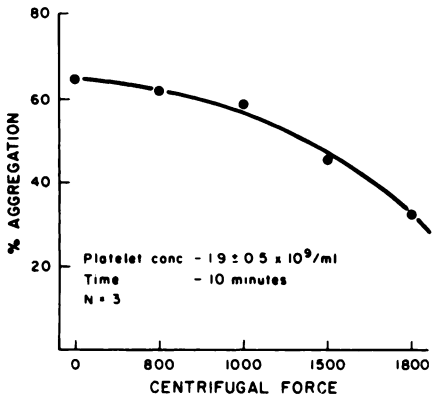

FIG. 4. Influence of centrifugal force (*g*) on aggregation of human platelets (see text for procedure).

that excess of oxine, but not of EDTA, causes the release of In-111 from labeled platelets (and leukocytes) provides further evidence that oxine penetrates the cell membrane. A major proportion of oxine does not remain cell-bound (*20,21*) and it is therefore conceivable that, at higher concentrations, oxine may adversely deplete cells of some metal ions and may affect the cell function.

Haunt and Cowan (*22*) have shown that ingestion of ethanol produced a decrease in platelet aggregability and impairment of both primary and secondary response to ADP. However, no quantitation was reported. In our observation, up to 15 μl of ethanol (1.5%, three times the normal concentration) per ml of (1.5×10^9) platelet suspension caused no apparent damage. This is true until the final ethanol concentration reaches 10% (*13*).

Thorburn (*23*) has reported failure of blood-clot formation and reduction in platelet aggregability in subjects receiving high doses of radiation. The exact mechanism of this phenomenon is unknown. In an in vitro situation, when 10^9 platelets are labeled with 100 μCi of In-111, each platelet receives a dose estimated at 14,500 rads (*14*). Yet platelets labeled with 2.5 times normal radioactivity (100 μCi/10^9 platelets in 1 ml) had normal aggregability. This remarkable resistance of platelets to the damaging effects of ionizing radiation appears to parallel that of human neutrophils, which have indicated no functional impairment at high radiation dose (*17*).

The adverse influence of centrifugal force on platelet aggregation was clearly seen. This observation is in agreement with Sixma's report (*25*) that improper centrifugation may cause platelet destruction and result in release of nucleotides that could change platelet reactivity irrespective of the population of platelets present.

Approximately 70% of the radioactivity is weakly bound to cytoplasmic components (*21*). This may be released by excessive oxine. Five to 20% of the radioactivity is associated with dense bodies (*26*). Upon aggregation, however, only 2.8% (1.4-3.6%) of the radioactivity is released. This agrees with the earlier reports by Joist et al. (*27*) and Hawker et al. (*14*).

Although the potential of In-111 platelets in imaging experimental thrombotic processes has been successfully demonstrated in laboratory animals, experiments using In-111 platelets in noninvasive clinical diagnosis and in the studies of in vivo platelet kinetics have thus far been preliminary (*9,28-32*). Antithrombotic agents, such as heparin, and nonsteroidal anti-inflammatory drugs, such as aspirin, indomethacin, propranolol, and chlorpromazine, are known to have adverse effect on platelet reactivity in vivo. Aspirin and indomethacin prolong bleeding time in normal subjects and severely aggravate the problems of patients with bleeding disorders (*33*). The influence of such agents on the potential use of In-111-labeled platelets for in vivo imaging remains to be systematically assessed. The simplicity of this improved method, which produces viable human platelets with an efficient incorporation of In-111, encourages its use for such studies and many other applications in which platelets play a major role.

FOOTNOTES

* Falcon.

† Diagnostic Isotopes: 1 mCi In-111 and 50 μg oxine in 50 μl ethanol.

‡ Chronolog.

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