Prognostic Significance of Late Imaging Results in Technetium-99m-Labeled Red Blood Cell Gastrointestinal Bleeding Studies with Early Negative Images

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The prognostic significance of the results of late imaging in patients with early negative ^{99m}Tc-labeled red blood cell (RBC) gastrointestinal (GI) bleeding studies was examined in a retrospective review of studies performed on 48 patients. Twenty-two studies showed intraluminal accumulation of labeled RBCs only on late images acquired from 3–24 hr following RBC injection. Patients with late positive studies had larger transfusion requirements than those with negative late images (mean total units transfused: 7.3 versus 3.5 ($p < 0.05$); mean units transfused following scan commencement: 4.5 versus 2.0 ($p < 0.005$)). Patients with late positive studies more frequently required angiography (3/22 versus 0/26) and surgery (5/22 versus 2/26). Sites of bleeding were more commonly identified in the stomach or small bowel in patients with late positive studies, while colon bleeding sources were more commonly found in those with late negative studies. The location of intraluminal blood on late images did not reliably discriminate upper from lower tract hemorrhage. In patients with early negative GI bleeding studies, results of later imaging provide objective evidence of the presence or absence of continued intermittent hemorrhage, and suggest both the region of bowel responsible and the relative risk for requiring further invasive procedures.

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Technetium-99m-labeled red blood cell (RBC) scintigraphy is widely used for investigation of patients with gastrointestinal (GI) hemorrhage of unknown etiology (*1–7*). The site of active hemorrhage can be accurately identified when a focal intraluminal accumulation of labeled RBCs is seen early after injection, followed by a characteristic pattern of progression of activity in the bowel on subsequent images (*2–7*). However, because of the intermittent nature of GI hemorrhage, more than 70% of labeled RBC scintiscans do not demonstrate a site of active hemorrhage during the first hour of imaging (*2,4,6*). While continuation of imaging beyond 1 hr results in more than 60% of all positive bleeding studies (*2,4,6*), unless frequent serial images have been obtained, it may not be possible to identify the exact bleeding site, given that ante- and retrograde movement of intraluminal RBCs can occur within minutes after an episode of acute hemorrhage (*3,8, 9*). Although most reports concerning RBC GI bleeding scintigraphy have noted the importance of late delayed imaging (*1,2,4–7*), the relationship between the findings on these images and ultimate diagnoses and clinical outcome have generally not been examined in detail.

We performed a retrospective review of GI bleeding studies performed at our institution during a 5-yr interval. This report describes our results for patients with early negative studies, most of whom had late delayed imaging. We compared transfusion requirements, hospital course, and clinical outcome between patients whose late images did and did not show evidence of GI hemorrhage. A small group of patients with early negative and no late images was examined as a potential validation set.

METHODS

One hundred six consecutive GI bleeding studies with ^{99m}Tc-labeled RBCs performed during a 5-yr period were retrospectively reviewed. All studies were acquired on large field of view gamma cameras using all-purpose or high-resolution collimators. Red blood cells were labeled with 740-925 MBq of ^{99m}Tc by the modified in vitro method (*10*). With the camera positioned over the anterior abdomen, flow images at 3–4 sec per frame were obtained for the first 60 sec following injection of the labeled cells. Thereafter, sequential anterior abdominal images were obtained every 5 min for 60–90 min, with additional anterior oblique and lateral views obtained as clinically appropriate. Of the 106 studies reviewed, 31 showed intraluminal accumulation of labeled RBCs in the bowel during the initial imaging session. Sixteen studies were terminated after 60–90 min without identification of a site of bleeding, while 59 other studies had additional delayed images acquired between 3 and 30 hr postinjection. The scan of one patient whose medical records could not be located was excluded, leaving 74 studies as the source material for the present report.

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The 74 studies that did not show evidence of GI hemorrhage during the initial imaging session were performed on 61 patients. Four patients were studied twice, two three times, and one six times during the period under review. Patients were predominantly male (n = 59), ranging in age from 21–90 yr (mean 59). All late positive images were confirmed on review by an experienced nuclear medicine physician (AFJ).

Inpatient and subsequent outpatient records were reviewed for each patient. The presentation of GI bleeding and an estimate of its duration prior to the patient's initial evaluation were recorded. Transfusions (whole blood and packed cells) administered during the entire bleeding episode and subsequent to commencement of the labeled RBC study were tabulated. For the purposes of these determinations, a bleeding episode was considered terminated following: 3 inpatient days with stable hematocrit and no transfusions; surgical or angiographic intervention to halt bleeding; hospital discharge; or death. For bleeding episodes which occurred in the course of prolonged hospitalizations for chronic illnesses, only the events which immediately preceded the initiation of the diagnostic workup for GI blood loss were considered. Length of hospital stay was recorded for the 34 patients who were admitted primarily for investigation of GI blood loss and whose hospitalizations were not extended by subsequent treatment for unrelated conditions.

Among the patients studied more than once, one had three and two had two RBC scans during single hospitalizations. For these three patients, two had late positive studies and were categorized according to those results. Four patients were studied during two or more hospitalizations, including one patient studied six times during a year for recurrent bleeding from an unidentified source. As all available data for these latter four patients suggested that each had one source responsible for the several episodes of GI hemorrhage, results for only one hospitalization were included in the present tabulations, the initial hospitalization in three and the second for one patient whose earlier scintigraphy did not include late images.

Thirty-eight bleeding sites were identified based upon results of colonoscopy (n = 14), esophagogastroduodenoscopy (EGD) (n = 9), surgery (n = 6), autopsy (n = 5), sigmoidoscopy (n = 2), and angiography (n = 2). Identification was considered definite in 19 patients with bleeding observed visually or angiographically, or who had a lesion with stigmata of recent hemorrhage, including a localized adherent clot or surrounding hyperemia. Nineteen bleeding sites were considered probable where lesions were identified in regions of suspected hemorrhage for which more definite visual or imaging evidence of recent hemorrhage was lacking. No specific bleeding site was identified in 23 patients, including 4 patients with thrombocytopenia, anticoagulant use, or coagulation disorders secondary to liver disease, and 3 patients on hemodialysis for renal failure.

Statistical Analysis

Statistical comparisons were performed using chi-square and Student's t-tests. A p value <0.05 was considered significant.

RESULTS

The initial clinical presentations of the patients in the present review are summarized in Table 1. Melena was the most common presenting complaint among patients with late positive studies, while passage of blood per rectum was the initial presentation among the majority of patients with late negative and no late imaging. Most patients sought medical attention within two days of observing evidence of GI bleeding.

Of the 48 patients whose studies did not demonstrate active bleeding during the first 60–90 min and who underwent later delayed imaging, intraluminal accumulation of labeled RBCs was seen in 22 (46%). Four of these patients had intermediate negative images at 2–6.5 hr postinjection. Time of first images positive for intraluminal blood ranged from 3 to 24 hr postinjection (mean 13 hr). Of the 22 late positive studies, 15 demonstrated activity exclusively in the cecum or colon (Fig. 1), 6 showed activity only in the stomach and/or small bowel (Fig. 2), and 1 showed activity in both small and large intestines. The pattern of accumulation of labeled RBCs suggested a likely site of bleeding in seven cases (Fig. 1).

Twenty-six patients had late images from 4 to 30 hr postinjection (mean: 18 hr) which showed no evidence of interval GI bleeding.

Transfusion data, interventional procedures, and duration of hospitalization are summarized in Figures 3 and 4. Patients with late positive studies had significantly larger total and post-study transfusion requirements and more frequently required angiographic and/or surgical intervention to locate and control bleeding. Total duration of

TABLE 1
Initial Presentation of GI Bleeding in 61 Patients with No Evidence of Bleeding on Early Labeled RBC Scintigraphic Imaging

Scintigraphic result	Presentation and duration							
	Melena		Blood per rectum		Guaiac positive stool		Other	
	0–2 days	>2 days	0–2 days	>2 days	0–2 days	>2 days	0–2 days	>2 days
Late positive	6	4	6	0	2	3	1*	0
Late negative	6	2	11	5	2	0	0	0
No late images	0	1	4	4	2	1	0	1†
Totals	12	7	21	9	6	4	1	1

* Both melena and blood per rectum.
† Blood per nasogastric tube.

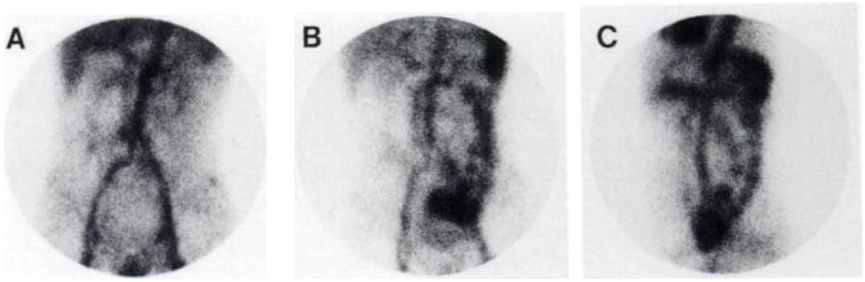

FIGURE 1. GI bleeding scan from 55-yr-old male with recurrent passage of bright red blood per rectum shows no abnormal accumulation of activity at 60 min postinjection (A). Anterior (B) and left lateral (C) images at 3.5 hr show prominent intraluminal activity in the transverse and left colon, with lesser activity in the right colon. Colonoscopy revealed numerous right and left colon diverticula, but no definite bleeding site. Subsequent subtotal colectomy identified a hyperemic diverticulum in the proximal ascending colon as the bleeding site.

hospitalization also tended to be longer among patients with late positive studies.

There was an association between the results of late imaging and the location of GI bleeding sites subsequently identified. In patients with positive late studies, the site of bleeding was more likely to be in the stomach or small bowel (9 of 15 identified), while in patients with no active bleeding identified on late imaging, the majority of bleeding sites identified (15 of 18) were in the colon ($p < 0.05$) (Fig. 5). Certainty of identification tended to be greater in the late positive group, with 67% (10/15) in the definite category compared with 50% (9/18) among those with late negative studies. Colon bleeding sites were most often identified on colonoscopy, while upper GI sources were usually documented at EGD, in the course of surgical exploration, or at autopsy. The frequency with which no specific bleeding site could ultimately be identified was similar among patients with positive and negative late images (7/22 versus 8/26, p = ns).

Among the 13 patients with no late images, there were two distinct groups with respect to transfusion requirements. Seven patients had total and post-scan transfusion ranges of 2–5 and 0–3 units, respectively (Fig. 6). Transfusion requirements for the remaining six patients were 12–24 and 3–20 units, respectively. Although none of the 13 patients underwent either angiography or surgery, three patients in the high transfusion group died within 3 wk of the GI bleeding studies from causes related to mesenteric ischemia, chronic graft-versus-host disease, and cardiorespiratory failure, respectively. Overall, a probable bleeding site was only identified in five patients, three in the high and two in the low transfusion group.

DISCUSSION

The major advantage of ^{99m}Tc-labeled RBCs over sulfur colloid for identification of sites of GI bleeding is the substantially longer opportunity for imaging (*11,12*). While active bleeding must occur within the first 10 to 15 min following injection of ^{99m}Tc-labeled colloid in order for the images to demonstrate extravasated blood, scintigraphy with labeled RBCs can be carried out for as long as there is sufficient activity to detect a localized accumulation of extravasated cells, generally about 24 hr (*1–7,11, 12*). Unfortunately, regardless of the agent used, the intermittent nature of GI hemorrhage and the unreliability of external signs for identifying when active bleeding is occurring pose significant obstacles to identification of a bleeding source (*14*). The initial period of imaging with labeled RBCs often must be terminated based upon practical limitations concerning the length of time unstable patients can be continuously studied in the absence of a positive finding. Once initial imaging has been terminated, decisions concerning when further imaging is performed usually reflect a compromise between the desirability of obtaining frequent images in order to pinpoint the first evidence of new RBC extravasation and practical considerations regarding patient safety and stability, camera availability, and time of day. Although imaging every 30–60 min for as long as necessary would provide the highest sensitivity for identification of active or renewed bleeding, this is generally not practical. Patients injected in the morning can usually be reimaged several times during the day, but for patients whose studies are begun in the late afternoon or evening, in the absence of obviously increased

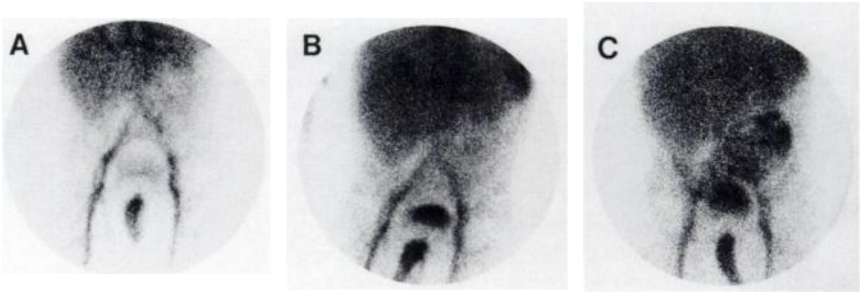

FIGURE 2. Sixty-minute (A) and 6.5-hr (B) anterior abdominal images of patient with melena do not demonstrate definite extravasation of labeled RBCs. A further delayed image at 24 hr (C) demonstrates diffuse activity throughout the small bowel. Subsequent EGD revealed diffuse gastritis with shallow ulcerations and blood in the body and antrum of the stomach.

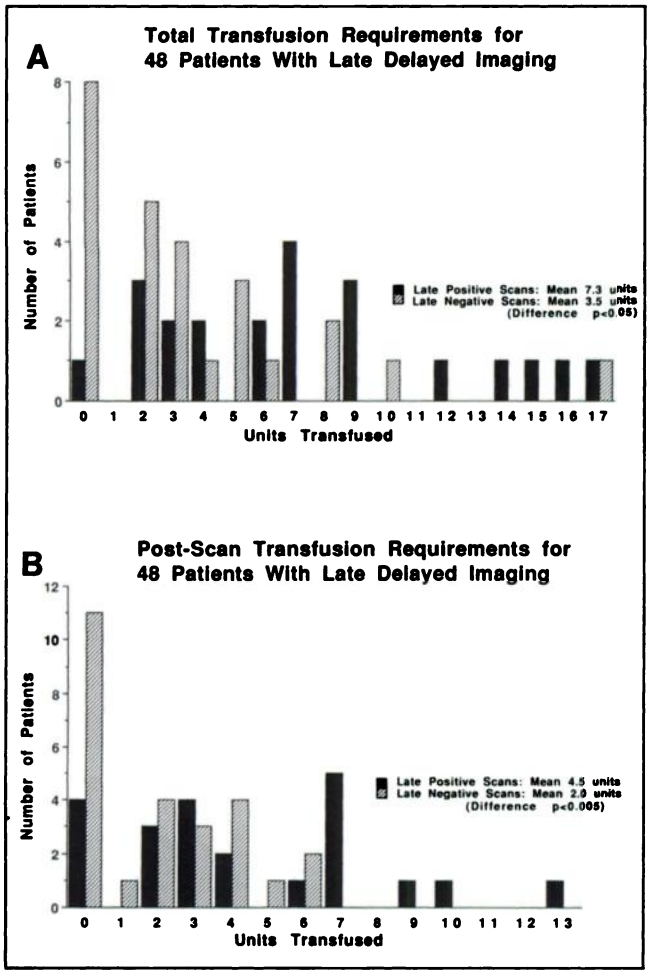

FIGURE 3. Transfusions received by 48 patients with early negative and later delayed GI bleeding scan images. (A) Total during bleeding episode. (B) Units transfused following time of scan commencement.

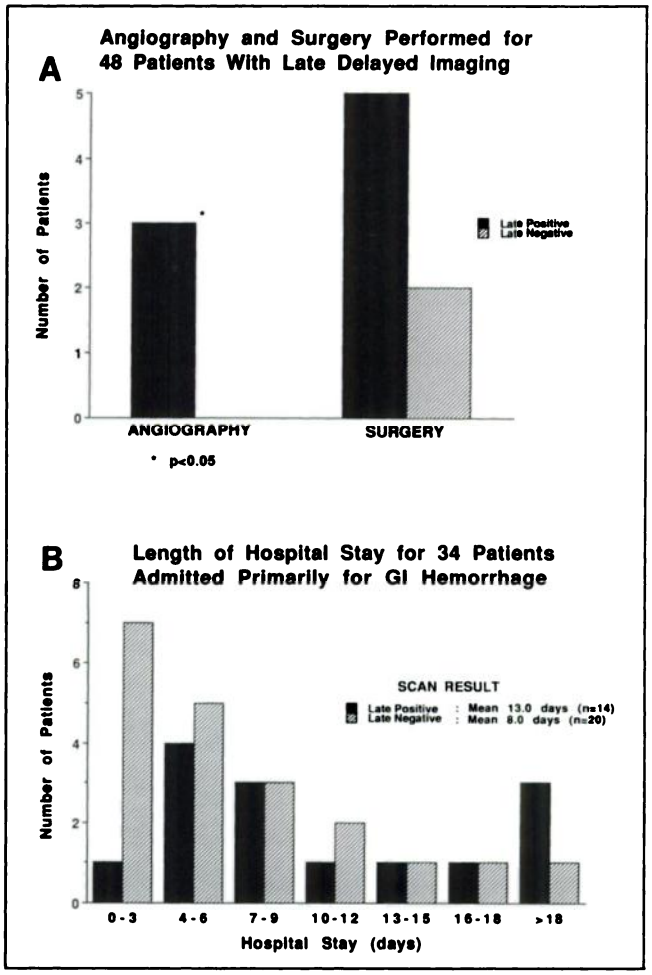

FIGURE 4. (A) Number of patients who underwent angiography or surgery among 48 patients with late delayed imaging. (B) Mean length of hospitalization for 34 patients admitted specifically for evaluation of GI hemorrhage.

or renewed bleeding, further imaging is usually performed the following morning. If clinical evidence suggests that bleeding has stopped, there is an inherent tendency to forego later imaging altogether.

The 46% prevalence of positive late delayed imaging among patients with early negative scans in the current study is similar to that reported in previous retrospective reviews of GI bleeding scintigraphy (*2,5,6*). The greater blood transfusion requirements for patients with delayed positive studies also have been previously observed (*2,5, 6*). The finding that patients with late positive studies more commonly had bleeding sources identified in the upper GI tract may in part reflect differences in the detectability of slow small and large bowel hemorrhage. Due to the smaller caliber and more extensive distribution of the small bowel, intraluminal RBC activity from a slow or intermittent bleeding site may not localize but may produce instead a diffuse abdominal "blush" not readily detectable above the intravascular blood-pool background. Of nine studies with upper GI bleeding sites and late positive images, six showed activity predominantly in the colon, tending to confirm the greater difficulty in initial identification of intraluminal labeled RBCs in the small bowel. The longer time required for blood to traverse both the small and large bowel, than the large bowel alone, also increases the likelihood that intermittent upper GI hemorrhage would result in late positive imaging more frequently than would comparable colonic bleeding. These technical factors aside, it remains clear that patients with late positive images had bleeding sites of greater clinical consequence, whether in the small or large bowel. Of 16 patients with total transfusions of 7 or more units, 12 had late positive studies, 11 of which had bleeding sites identified, 6 in the stomach or small bowel and 5 in the colon.

Retrospective review has obvious limitations as a means for assessing the utility of GI bleeding imaging performed beyond the initial continuous 60–90 min of acquisition. The times at which delayed images were acquired were determined by clinical considerations and logistical issues related to the time the study was begun, whether during

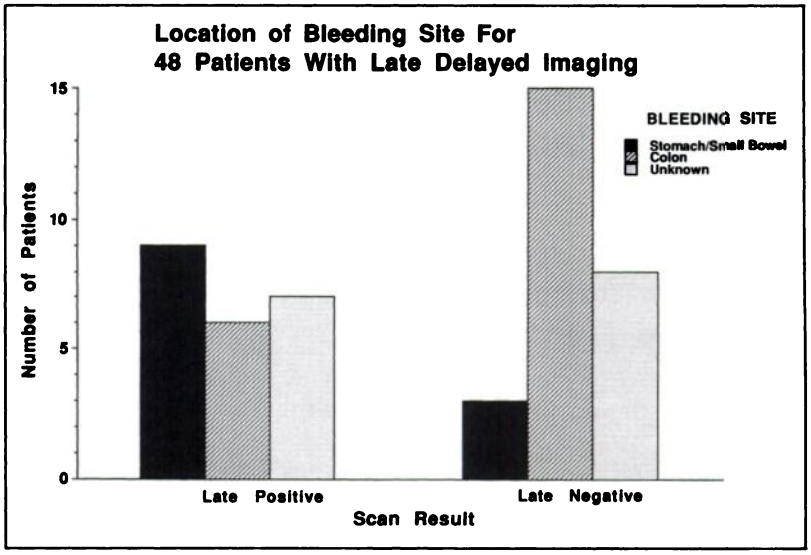

FIGURE 5. Location of bleeding sites identified for 48 patients with late delayed imaging.

the day or at night. As such, the results presented here cannot establish the earliest time when any given study might have been positive, which would require imaging of the abdomen every 15–30 min throughout the 24-hr period. Nevertheless, our findings reflect the realities of imaging and clinical management of patients with occult GI bleeding.

The major implication of our results concerns the prognostic utility of delayed GI bleeding scan images. These later images provide a partial measure of the cumulative blood loss during the interval since injection of the radiolabeled cells (*15*), objective evidence of continued active bleeding which should be more reliable than either persistent melena, which might be the result of a bleeding episode which occurred many hours earlier, or an interval decrease in hematocrit, which may be seen as a result of hemodilution from intravenous fluids even after bleeding has stopped. Reliable documentation of continued hemorrhage is particularly important for bleeding sites in the small bowel, which are beyond the access of conventional endoscopy. In the present series, patients with late positive studies more commonly presented with melena and had upper GI bleeding sites identified, including two in the small bowel beyond the duodenum. By comparison, most patients with negative late images presented with passage of blood per rectum and had bleeding sites within the range of a sigmoidoscope or colonscope.

The findings in the 13 patients who did not undergo later delayed imaging tend to confirm the findings in the 48 who did. There were two distinct groups of patients, equal in size but quite different in clinical outcome. Seven patients had low transfusion requirements and generally short and uncomplicated hospital courses with respect to management of GI hemorrhage. Six other patients required 3–5 times as much blood replacement, and three died during the hospitalizations, including two patients with involvement of large segments of small and/or large bowel, one secondary to ischemia and the other as a result of chronic graft-versus-host disease. The absence of either angiography or surgery in this latter group reflects, in part, multi-organ disease involvement or preterminal conditions which rendered these interventions either impractical, too dangerous, or moot.

Ideally, late delayed imaging should be obtained at multiple time points, but this is usually only readily accomplished for studies begun in the morning. At the minimum, imaging should be performed the morning following the day of the original injection. Should results of late imaging suggest that bleeding is occurring at that time, but the count rate is inadequate to localize the bleeding site precisely, use of a second labeled RBC injection, which we previously reported may on occasion allow identification of the bleeding site (*16*), can also be considered.

Approximately 70% of labeled RBC GI bleeding studies in this review failed to demonstrate a site of active hemorrhage during the initial 1–2 hr of imaging. Without evidence of extravasation during early imaging, identification of the site of active GI hemorrhage is difficult (*16–18*). In spite of the limitations of ^{99m}Tc-labeled RBC scintigraphy, if the study is not positive during the initial imaging session, this method still provides the potential for later identification of a bleeding site which cannot be achieved with any other modality. Even in patients with early positive RBC scintigraphy, a significant proportion will have follow-up angiography which is unable to identify a site of active bleeding (*2,4,7*). While late delayed scintigraphy can sometimes provide an indication that a discrete region of bowel contains the bleeding site, the present results suggest prognostic and diagnostic roles for these images even in the absence of such findings. Positive late imaging identifies patients who are more likely to continue to have GI blood loss, thereby providing the impetus for more aggressive volume and blood replacement and diag-

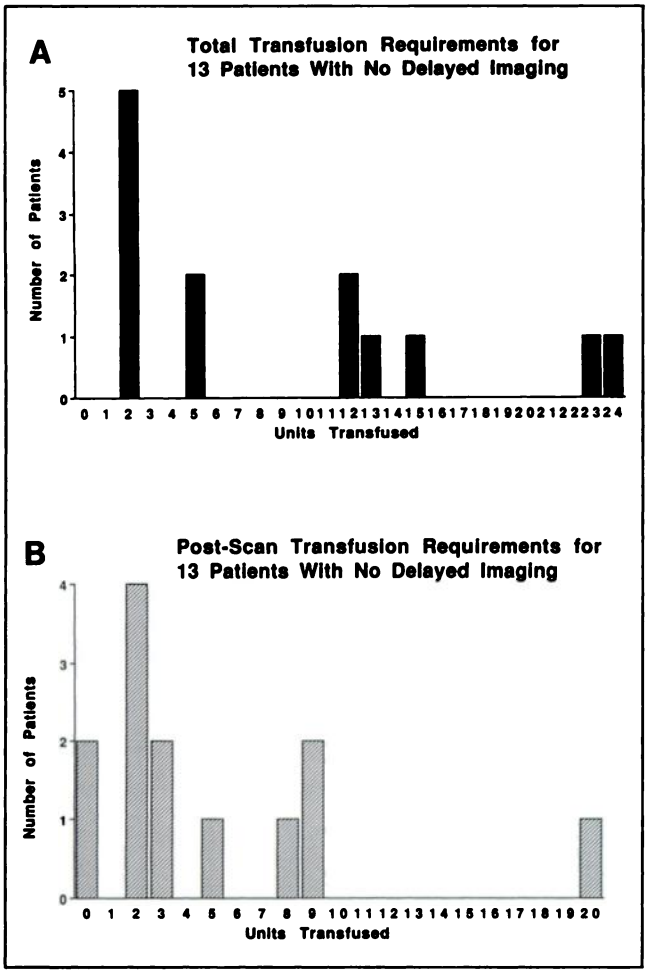

FIGURE 6. Total (A) and post-scan (B) transfusion requirements for 13 patients with early negative and no later GI bleeding scan images.

nostic investigations, especially in the stomach and small bowel. Conversely, negative late imaging makes an upper GI bleeding site unlikely and provides the expectation of an uncomplicated hospital course. The possibility that hemodynamically stable patients with 24-hr scintigraphic studies without evidence of active GI hemorrhage could be discharged earlier and have part of their diagnostic evaluation (e.g., colonoscopy, barium enema) performed as outpatients may warrant further investigation.

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