Time to endoscopy and outcomes in upper gastrointestinal bleeding

Nitin Sarin MD FRCPC, Neerav Monga MSc, Paul C Adams MD FRCPC

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BACKGROUND: Upper gastrointestinal bleeding (UGIB) is a common problem associated with significant morbidity and mortality. Previous studies show that immediate endoscopies do not affect outcomes in patients; however, endoscopic interventions have evolved. The present retrospective review of endoscopies performed at a large teaching hospital assessed the timing of endoscopy with respect to the morbidity and mortality of UGIB.

METHODS: Diagnostic billing codes were used to assess all inpatients of gastroenterologists at the University Hospital of the London Health Sciences Centre, London, Ontario, from July 2004 to June 2006, using a centralized data recording system. Time to endoscopy (within 6 h, 6 h to 24 h and beyond 24 h) were compared for the outcomes of mortality, need for surgery and transfusion requirements.

RESULTS: From July 2004 to June 2006, there were 502 upper endoscopies performed for the indication of suspected UGIB and 375 for overt acute nonvariceal UGIB. Approximately 10% of cases revealed variceal bleeding. When comparing endoscopy within 6 h with endoscopy at 6 h to 24 h, there were no significant differences in mortality, need for surgery (OR 3.6 and 2.8, respectively, compared with endoscopy beyond 24 h) or transfusion requirements. Even when assessing the group that received endoscopic hemostasis, time to endoscopy was not associated with better outcomes. Multivariate analysis did not demonstrate any advantages for early endoscopy (less than 6 h) compared with endoscopy within 24 h.

CONCLUSIONS: Most patients with acute gastrointestinal bleeding can be effectively managed with endoscopy within 24 h.

Key Words: *Endoscopy; Gastrointestinal hemorrhage; Gastroscopy; Peptic ulcer hemorrhage*

Hémorragie digestive haute : temps écoulé avant l'endoscopie et résultats cliniques

CONTEXTE : L'hémorragie digestive haute (HDH) est un trouble fréquent, lié à une morbidité et à une mortalité élevées. D'après des études antérieures, l'endoscopie immédiate n'a pas d'incidence sur les résultats cliniques, mais les techniques endoscopiques ont évolué. Nous avons donc entrepris le présent examen rétrospectif des endoscopies pratiquées dans un grand hôpital d'enseignement afin d'évaluer la morbidité et la mortalité attribuables aux HDH en fonction du temps écoulé avant l'endoscopie.

MÉTHODE : Les codes de facturation d'examens diagnostiques, tirés d'un système centralisé d'enregistrement des données, ont servi à l'évaluation de tous les malades hospitalisés, traités par des gastroentérologues rattachés à l'University Hospital of the London Health Sciences Centre, à London, en Ontario, de juillet 2004 à juin 2006. Nous avons comparé le temps écoulé avant l'endoscopie (moins de 6 h, de 6 h à 24 h, plus de 24 h) avec la mortalité, la chirurgie et les transfusions.

RÉSULTATS : De juillet 2004 à juin 2006, 502 endoscopies hautes ont été pratiquées pour une HDH présumée et 375, pour une HDH non variqueuse aiguë, franche. Dix pour cent des cas environ se sont révélés d'origine variqueuse. Dans les comparaisons entre l'endoscopie pratiquée en moins de 6 h et l'endoscopie pratiquée de 6 h à 24 h, il n'y avait pas d'écart important en ce qui concerne la mortalité, la chirurgie (salle d'opération : 3,6 et 2,8, respectivement, par rapport à l'endoscopie après plus de 24 h) et les transfusions. Même dans le groupe soumis à l'hémostase endoscopique, le temps écoulé avant l'endoscopie n'était pas associé à de meilleurs résultats cliniques que ceux motés dans les autres groupes. Par ailleurs, d'après l'analyse pluridimensionnelle, l'endoscopie précoce (moins de 6 h) ne se montrait pas plus salutaire que l'endoscopie pratiquée dans les 24 h.

CONCLUSION : La plupart des patients souffrant d'une hémorragie digestive aiguë peuvent être traités efficacement par endoscopie dans les 24 h.

Upper gastrointestinal bleeding (UGIB) is a major indication for hospital admissions in North America (1), and a common indication for inpatient endoscopic procedures. Many episodes may be self-limited, but there are significant morbidity and mortality rates (5% to 10%) associated with bleeding episodes (2). Interestingly, although there have been therapeutic advances in endoscopic hemostasis and advances in medical therapies for ulcer bleeding, mortality rates have not significantly changed in the past decades (2).

Currently, guidelines support the use of upper endoscopy within 24 h for patients presenting with UGIB (3). The advantages of undergoing earlier endoscopy include achieving hemostasis more quickly, possibly preventing complications, decreasing transfusions and length of hospital stay for these patients (3-5). Aggressive resuscitation has shown a mortality benefit in the setting of UGIB. (6). Meta-analyses and reviews (7,8) suggest a significant benefit of endoscopy and proton pump inhibitor use, particularly for ulcers with active bleeding or high-risk stigmata for bleeding. However, the optimal timing for endoscopy has not been clearly established.

The performance and timing of endoscopy is highly variable and may depend on patient characteristics, as well as timing of presentation, timing of referral to endoscopist and availability of endoscopic facilities. If there is a benefit to earlier endoscopy, which could achieve earlier hemostasis and potentially decrease morbidity and mortality, then time to endoscopy would be an independent predictor of improved patient outcomes. If rapid endoscopy is beneficial, it may place significant burdens on hospital care providers to provide active 24 h endoscopic coverage and necessitate urgent transfers of patients to centres with endoscopy units during off-hours periods.

Department of Medicine, University of Western Ontario, London, Ontario
Correspondence: Dr Paul C Adams, Department of Medicine, University Hospital, 339 Windermere Road, London, Ontario N6A 5A5.
Telephone 519-685-8500 ext 35375, fax 519-663-3549, e-mail padams@uwo.ca
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TABLE 1
Patient demographics

Characteristics	Time to endoscopy <6 h (n=72)	6 h to 24 h (n=198)	>24 h (n=232)	Total (n=502)
Age, years (mean ± SD)	64.7±14.7	68.8±14.9	67.2±6.2	71.3±13.3
Men	50 (69)	289 (57)	113 (57)	125 (54)
Previous bleed	18 (25)	123 (25)	56 (28)	48 (21)
Rockall comorbidity score				
0 (none)	13 (18)	177 (35)	81 (41)	83 (36)
2 (active comorbidity)	25 (35)	181 (36)	63 (32)	93 (40)
3 (renal failure, metastatic cancer)	34 (47)	142 (28)	52 (27)	55 (24)
Liver disease/cirrhosis	29 (40)	90 (18)	36 (18)	25 (11)
Vital signs				
Stable	31 (43)	323 (65)	115 (58)	176 (77)
Tachycardic	14 (19)	111 (22)	59 (30)	38 (17)
Hypotensive	27 (38)	66 (13)	23 (12)	16 (7)
Intensive care unit patient	15 (21)	43 (9)	17 (9)	11 (5)
Admitting diagnosis (not gastrointestinal bleed)	22 (31)	162 (32)	93 (22)	47 (42)
Symptom				
Nonovert bleeding	6 (8)	84 (17)	19 (9)	59 (26)
Melena	14 (19)	186 (37)	86 (43)	86 (37)
Coffee ground emesis	15 (21)	106 (21)	49 (25)	42 (18)
Hematemesis	25 (35)	77 (15)	27 (14)	25 (11)
Bright red blood per rectum + hypotension or syncope	12 (17)	49 (10)	17 (9)	19 (8)
Previous drugs				
Proton pump inhibitor	29 (40)	153 (31)	61 (31)	63 (27)
Antiplatelet (acetylsalicyclic acid, NSAIDs, clopidogrel)	30 (42)	286 (57)	111 (56)	145 (63)
Anticoagulant (coumadin, heparin)	14 (19)	99 (20)	35 (18)	50 (22)
Laboratory results				
Mild coagulapathy	35 (49)	142 (29)	45 (23)	61 (27)
Severe coagulopathy	6 (8)	39 (8)	11 (6)	22 (10)
Hemoglobin at presentation, g/L (mean ± SD)	84±25	94±28	94±29	97±26
Platelet count at presentation, $\times 10^9$/L (mean ± SD)	222±145	261±137	257±119	277±144
Time to proton pump inhibition/octreotide, h (mean ± SD)	2.0±2.0	4.1±19	5.7±6.7	16±27
Variceal bleed	18 (25)	49 (10)	19 (10)	12 (5)

Data presented as n (%) unless otherwise indicated. NSAIDs Nonsteroidal anti-inflammatory drugs

The aim of the present study was to investigate all upper endoscopies performed for suspected UGIB, and assess the effect of time to endoscopy on patient outcomes.

METHODS

Data collection

A retrospective chart review was performed on all inpatient and emergency room upper endoscopies performed from July 2004 to June 2006 at the University Hospital of the London Health Sciences Centre, London, Ontario. Inpatient gastroenterology teams are rotated among five staff gastroenterologists, as well as residents and fellows. Attending physicians are present at all endoscopies. Patients were identified based on the Ontario schedule of benefits codes for upper endoscopy within an inpatient setting.

All patients older than 18 years of age who received upper endoscopies for suspected UGIB were included in the study. Patients were excluded from the present study if the indication for upper endoscopy was not related to suspected active UGIB. The common nonbleeding indications included dysphagia, screening for portal hypertension or cirrhosis, food impactions and chronic anemia.

Time to endoscopy was calculated from presentation to emergency room with a bleed or the first documentation of overt bleeding if it occurred in an inpatient. A Rockall comorbidity scale was used for assessing the severity of comorbidities (9). Tachycardia was defined by a heart rate of more than 100 beats/min; hypotension was defined by a heart rate of more than 100 beats/min with a systolic blood pressure of less than 100 mmHg, or systolic blood pressure of 80 mmHg or less, or inotrope use. Significant coagulopathy was defined as an international normalized ratio of more than 3.0, and moderate coagulopathy was defined as an international normalized ratio of 1.3 to 2.9.

Data abstraction

A standardized form with a single data extractor was used to abstract the data from a combination of endoscopy records, electronic patient records and hospital charts. Demographic data, endoscopic findings and patient outcomes up to 30 days

TABLE 2
Outcomes versus time to endoscopy

Outcome measures	Time to endoscopy			Total (n=502)
	<6 h (n=72)	6 h to 24 h (n=198)	>24 h (n=232)	
Intervention	38 (53)	116 (23)	52 (26)	26 (11)
Mortality (30-day)	16 (22)	51 (10)	23 (12)	12 (5)
Surgery	9 (13)	29 (6)	12 (6)	8 (3)
Transfusions, n				
>5	31 (43)	90 (18)	34 (17)	26 (11)
3 to 5	17 (24)	113 (23)	53 (27)	43 (19)
1 to 2	11 (15)	130 (26)	55 (28)	64 (28)
0	13 (18)	167 (33)	56 (28)	98 (42)
Repeat endsocopy within 48 h	16 (22)	42 (8.4)	20 (10)	6 (3)
Inadequate visualization	28 (39)	65 (11.3)	28 (14)	9 (4)
Length of hospital stay, days (median ± SD)	5.2±12	5.0±10.6	4.3±11	6.3±9

Data presented as n (%) unless indicated otherwise

were recorded. This process was approved by the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects. Endoscopic interventions included injection therapy (adrenaline, saline, alcohol), bipolar electrocoagulation, argon plasma coagulation, hemoclips and banding of esophageal varices.

Assessment of outcomes

Patients were separated into three groups – endoscopy within 6 h, endoscopy between 6 h to 24 h, and endoscopy more than 24 h from presentation to emergency room with bleed or first documented overt bleeding. The primary end point was the difference in mortality and the need for surgery to stop bleeding among these groups. The secondary outcome was the difference in transfusion requirements among these three groups.

Statistical methods

Multivariate logistic regression was used to analyze the primary outcome of adverse events comprised of all-cause mortality within 30 days of initial endoscopy and the need for surgical intervention for refractory bleeding. Transfusion requirement of packed red blood cells was used as a secondary outcome that was analyzed using multivariate logistic regression.

Automated checks were performed for data completion and inconsistencies were manually resolved with a review of medical records. Models with good fit were built examining overt acute nonvariceal UGIB for the primary outcome of mortality or need for surgery. A backward selection method was used. Forward and stepwise models were also built to check for appropriate variables and had concordance with relevant variables selected using the SAS/Stat Software version 9.1.3 (SAS Institute Inc, USA). Models were also built specifically for acute overt nonvariceal UGIB. A univariate analysis in the highest-risk group for those with active bleeding or visible vessel, or adherent clot receiving endoscopic hemostasis was performed examining time to endoscopy versus the primary outcome of mortality or need for surgery and the secondary outcome of transfusion requirements.

RESULTS

After initial review, 780 potential charts were identified. Sixteen were incomplete, leaving 764. After exclusion criteria were applied, 502 patient charts were identified as eligible for the present study. The demographic characteristics of the study group are presented in Table 1. Thus, approximately 66% of inpatient endoscopies were performed for suspected acute UGIB. In terms of overt acute nonvariceal UGIB, our primary group of interest with regard to timing of endoscopy, numbered 375 patients.

Table 2 shows the overall patient outcomes versus the time to endoscopy. In terms of outcomes, individuals who received endoscopy within 6 h of presentation were more likely to receive intervention and have higher transfusion requirements, but also more likely to require repeat endoscopies and have inadequate visualization of bleeding sources than those with endoscopies at more than 24 h from presentation. Lengths of hospital stay were not significantly different.

Table 3 shows the univariate analysis of risk factors for the primary outcome of interest – mortality or need for surgery. These factors were used for subsequent multivariate analysis model building.

The final multivariate model of independent risk factors for overt acute nonvariceal bleeding is shown in Table 4. This indicates that those having endoscopies within 6 h were 3.6 times more likely to require surgery or die than those who had endoscopy beyond 24 h (95% CI 1.4 to 9.4; P=0.008). Other significant predictors of mortality and requiring surgery were hypotension at presentation, severe comorbidities (ie, cirrhosis, renal failure or metastatic cancer) and older age. Of note, when comparing patients who underwent endoscopy within 24 h only, no significant difference was noted between endoscopy within 6 h (OR 3.6; 95% CI 1.4 to 9.4) and endoscopy within 6 h to 24 h (OR 2.8; 95% CI 1.3 to 6.2).

In the secondary analysis for transfusion requirements, time to endoscopy was not significantly associated with transfusion requirements. The only factors that predicted increased transfusion requirements were lower initial hemoglobin and hypotension at presentation (data not shown).

In the subgroup of patients who received endoscopic hemostasis for overt nonvariceal UGIB, there were 72 patients. Therapies included argon plasma coagulation in 10 patients, bipolar cautery with adrenaline injection in 24 patients, hemoclips with adrenaline injection in 17 patients and adrenaline injections alone in 21 patients. No factors were significantly associated with requiring surgery or 30-day mortality, or with

TABLE 3
Univariate analysis of predictors of mortality and surgery for acute nonvariceal upper gastrointestinal bleeds

Risk factor	Mortality and surgery rate		P
	With risk factor	Without risk factor	
Age, years (mean ± SD)	74±14	68±15	<0.001
Men	33/221 (15)	16/154 (10)	0.19
Previous bleed	10/88 (11)	39/287 (14)	0.59
Moderate comorbidity (Rockall comorbidity score 2 versus 0)	23/148 (16)	11/145 (8)	0.032
Severe comorbidity (Rockall comorbidity score 3 versus 0)	15/80 (19)	11/145 (8)	0.032
Liver disease/cirrhosis	4/39 (10.3)	45/336 (13.4)	0.58
Tachycardic versus stable vital signs	8/90 (9)	22/229 (10)	0.38
Hypotensive versus stable vital signs	19/54 (39)	22/229 (10)	<0.001
Inpatient bleed versus presentation to emergency room with gastrointestinal bleed	26/124 (21)	23/251 (10)	0.0052
Presenting symptom			
Coffee ground emesis versus melena	11/100 (11)	21/172 (12)	0.65
Hematemesis versus melena	10/58 (17)	21/172 (12)	0.65
Bright red blood per rectum with hemodynamic instability versus melena	7/45 (16)	21/172 (12)	0.65
On proton pump inhibitor at presentation	16/102 (16)	33/273 (12)	0.36
On antiplatelet or nonsteroidal anti-inflammatory drug therapy at presentation	28/226 (12)	21/149 (14)	0.63
On anticoagulant therapy at presentation	12/82 (15)	37/293 (13)	0.63
International normalized ratio 1.3 to 2.9 versus <1.3	17/89 (19)	24/253 (9)	0.0024
International normalized ratio >2.9 versus <1.3	8/27 (30)	24/253 (9)	0.0024
Hemoglobin at presentation, g/L (mean ± SD)	86±25	98±28	<0.001
Platelet count at presentation, $\times 10^9$/L (mean ± SD)	263±138	271±172	0.35
Time to endoscopy			
<6 h versus >24 h	14/49 (29)	11/163 (7)	<0.001
6 h to 24 h versus >24 h	24/162 (15)	11/163 (7)	<0.001
<6 h versus 6 h to 24 h	14/49 (29)	24/162 (15)	0.38

Data presented as n/n (%) unless indicated otherwise

TABLE 4
Predictors of mortality or surgery for acute nonvariceal upper gastrointestinal bleeding

Factors	OR	95% CI	P
Endoscopy within 6 h versus >24 h	3.6	1.4–9.4	0.008
Endoscopy at 6 h to 24 h versus >24 h	2.8	1.3–6.2	0.010
Age	1.05	1.02–1.08	0.003
Hypotensive versus stable vital signs	3.9	1.8–8.6	0.0006
Severe comorbid conditions versus no comorbid conditions	3.5	1.4–9.1	0.009

transfusion requirements. Specifically, timing to endoscopy – even in the group receiving endoscopic intervention – did not predict better outcomes in terms of surgery, mortality or transfusion requirements. This group is the most likely to receive benefit from early endoscopy; however, this small subset is likely underpowered to detect small differences in mortality, surgery or transfusion requirements.

DISCUSSION

Original studies that investigated the role of upper endoscopy and patient outcomes reported no change in management or patient outcomes; however, these studies were undertaken in an era when therapeutic endoscopy was less commonly used (10-12). Some studies (7,13) have shown a benefit to endoscopy and proton pump inhibition in high-risk bleed populations. Also, a large trial (14) suggests that intravenous proton pump inhibitors before endoscopy may lead to fewer active lesions requiring hemostasis and shorter lengths of stay, although patients with ongoing hemodynamic instability were excluded from this trial. Some retrospective reviews (5,14,15) have suggested that endoscopy within 24 h for active bleeding decreases rebleeding and lengths of stay. However, studies investigating endoscopy within 24 h (16,17) have shown no significant benefit to earlier versus later endoscopy.

Our results show that endoscopy within 6 h versus 6 h to 24 h, is not associated with any difference in patient outcomes in terms of mortality and need for surgery, or transfusion requirements in hospital patients presenting with acute nonvariceal UGIB. Patients receiving endoscopy within 24 h had poorer outcomes than those receiving endoscopy at more than 24 h; this likely relates to the severity of bleeds and patients who are more stable (ie, being able to wait longer than 24 h for endoscopy). Even when surveying our highest-risk group (ie, patients who required endoscopic hemostasis for bleeding lesions), there was no benefit in mortality, surgery or transfusion requirements from endoscopy performed within 6 h compared with endoscopy at 6 h to 24 h. Our results are consistent with other retrospective studies investigating the issue of rapid endoscopy (16,17).

Predictors that were significant for poorer outcomes in terms of mortality, surgery and transfusion requirements included hypotension at presentation, significant comorbidities as defined by renal failure, cirrhosis or metastatic cancer, and older age. It is possible that organizing rapid endoscopy within 6 h may slow intensive resuscitative efforts, early rescusitative efforts have

been shown to decrease mortality of UGIB patients (6). Also, visualization may be poorer and repeat endoscopies may be required. Early proton pump inhibition may also be beneficial (13). It has been suggested that rapid endoscopy can lead to more respiratory complications (18).

The current study shows that two-thirds of upper endoscopies performed on inpatients were for the indication of suspected acute UGIB. There does not appear to be any patient benefit to rapid endoscopy within 6 h compared with 6 h to 24 h. Many patients do wait longer than 24 h for suspected UGIB; in our population, this group did not have any adverse clinical outcomes. In fact, patients who had their endoscopies performed at more than 24 h had better clinical outcomes. Given the retrospective nature of the present study, this is limited by selection bias and is difficult to comment on. Patients able to wait longer than 24 h for endoscopy are likely more stable than patients who cannot wait. There are significant limitations to the present retrospective study. The allocation of endoscopy within 6 h, from 6 h to 24 h or longer than 24 h was not part of a randomized protocol; consequently, it is difficult to compare these groups. Patients who received early endoscopy were likely to have a more significant bleed, which leads to poorer patient outcomes. While we tried to account for variables that predicted the severity of the bleed, including patient comorbidities, age, initial hemoglobin and hemodynamic stability, it is still difficult to assess whether the timing of endoscopy is truly an important variable in patient outcomes without a prospective randomized trial. Our sample size may also not be sufficient to predict smaller differences in meaningful clinical outcomes.

Endoscopy within 6 h in the setting of acute nonvariceal UGIB in our population is not associated with decreased mortality, need for surgery or decreased transfusion requirements compared with endoscopy within 6 h to 24 h. Within the highest-risk subgroup of those with bleeds or lesions requiring endoscopic hemostatic intervention, there was still a trend toward worse outcomes with earlier endoscopy, although our sample size of 72 patients is underpowered to make any firm conclusions. Further prospective randomized studies are needed to shed light on the optimal timing of endoscopy for UGIB.

These observations have implications for providing resources for emergency endoscopy services. This usually includes an experienced nurse receiving overtime pay. Requests for emergency endoscopy often arise from junior house staff on other services such as surgery or critical care. Education of medical and paramedical personnel on the lack of efficacy of endoscopy within 6 h compared with 6 h to 24 h, is an important step in planning for the optimal use of hospital resources.

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