Poor outcomes after dabigatran-associated intracranial hemorrhage despite idarucizumab reversal

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ABSTRACT

Intracranial hemorrhage (ICH) is the most deadly bleeding complication associated with anticoagulation. The efficacy of idarucizumab in treating dabigatran-associated ICH in the real world is uncertain. We sought to assess patient outcomes in this sick population. This was a 2-year prospective observational study of functional neurologic status in patients who received idarucizumab following dabigatran-associated ICH across three tertiary Canadian hospitals. The primary outcome was disability on the modified Rankin scale thirty days after antidote administration. Five patients received idarucizumab for dabigatran-associated ICH. The median time to idarucizumab administration was 43 minutes (range: 2–163 minutes). Four patients were dead at 30 days. The fifth patient was in a minimally conscious state with hemiparesis requiring full nursing care. Three patients were transitioned to palliative care based on their advanced directives and dismal prognosis as determined by the treating team. High quality care should not include idarucizumab when it is unlikely to achieve patients’ previously stated goals of care. However, rapid administration of this expensive antidote is often necessary when information is incomplete.

INTRODUCTION

Intracranial hemorrhage (ICH) is the most deadly bleeding complication associated with anticoagulation from dabigatran, a direct thrombin inhibitor [1]. Idarucizumab is a humanized monoclonal antibody fragment against dabigatran that produces rapid reversal of coagulation parameters. While Health Canada approved idarucizumab in March 2016 for severe dabigatran-associated bleeding, its impact on clinical outcomes remains imprecise due to the lack of high quality randomized studies and uncertainty regarding the therapeutic window for its administration [2]. The decision to administer idarucizumab in clinical practice is further complicated by the drug’s high cost and perceived medicolegal risk to provider if withheld [3]. The effectiveness of idarucizumab in treating ICH likely differs from the results reported by a large industry-funded study such as Reversal of Dabigatran Anticoagulant Effect With Idarucizumab (RE-VERSE AD) [4]. We sought to assess patient outcomes following administration of the drug for ICH in clinical practice.

METHODS

Study design

This was a prospective, observational study of functional neurologic outcome following idarucizumab administration for ICH across 3 urban, academic Canadian hospitals between June 1, 2016 and June 1, 2018. Combined, these centers have 700 inpatient beds, 95,000 annual emergency patient visits, and referrals for specialized care in trauma, neurosurgery, and interventional neuroradiology. Ethics approval was obtained from the McGill University Health Centre institutional review board.

Study enrolment and data collection

Physicians ordering idarucizumab were required to submit an evaluation form with the following patient data to obtain pharmacy release of the drug: patient demographics, clinical indication for idarucizumab, and available coagulation parameters. All patients with ICH with a request for idarucizumab were included. There were no exclusion criteria. The
following data were collected for each patient on a
standardized data abstraction tool by two independent
reviewers who resolved discrepancy by consensus dis-
cussion: type of bleed, initial Glasgow coma scale
(GCS), partial thromboplastin time (PTT) before and
after idarucizumab administration, medications, renal
impairment, and time to idarucizumab administra-
tion. The primary outcome was functional neurologic
status at thirty days as assessed using the modified
Rankin Scale (mRS), a clinician-reported score of glo-
bal disability [5]. Patients who were discharged or
transferred before 30 days were followed by phone.

Analysis

The study population was small and non-parametric
descriptive statistics were used when appropriate.

Results

The pharmacy received 12 evaluation forms for idaru-
cizumab administration during the study period.
Seven requests were for non-ICH indications. Five
patients with ICH received idarucizumab and were
thus included in the study. Patients had both trau-
matic and spontaneous bleeds (Table 1). There was
100% follow-up and median mRS for patients at 30
days was 6 (range 5–6). All four patients enrolled
from the emergency department died despite present-
ing with initial GCS ≥ 12. The surviving patient was
enrolled from a medicine ward and remained hemipa-
retic in a minimally conscious state at 30 days.

The median time from emergency department
presentation or symptom onset to idarucizumab
administration was 43 minutes (range: 2–163 minutes).

The PTT was elevated in all patients upon presenta-
tion and normalized when repeated after antidote
administration. Patients 1 and 2 did not receive repeat
partial thromboplastin tests; one due to palliative care
choice by the family and the other due to transfer to
another institution. One patient (#1) was on concur-
rent aspirin therapy. Substitute decision makers for
patients 1, 2, and 4 requested palliative care within
2 hours of idarucizumab administration. Treating
teams believed the prognosis was dismal for each of
these patients based on the speed of clinical deterio-
ration and the extent of ICH on the initial scan.

Discussion

Our results suggest that patients who receive idaru-
cizumab for dabigatran-reversal in ICH fare poorly in
spite of normalized coagulation parameters. This con-
trasts the findings of RE-VERSE AD in which only 16
of 98 patients with ICH died at 30 days (16.4%).
Given the relationship between industry funding and
the reporting of positive findings, this discrepancy
raises questions about the effectiveness of idarucizu-
mab in clinical practice [6,7]. We could not compare
our functional neurologic outcomes with those of RE-
VERSE AD because of their incomplete reporting.
Many patients in our study had advanced directives
which resulted in early de-escalation of care. Each of
these decisions, however, occurred after discussion
with the treating physician and reflects the critical
intersection of individual patient values and medical
evidence. The treating teams did not believe the
patients were capable of achieving a meaningful
neurologic recovery based on rapid deterioration and
the initial imaging studies despite receiving

| Patient no. | Age (years) | Sex | Renal Impairment | Dabigatran Dose | Type of bleed | Initial GCS | Time to drug (min) | mRS at 30 days |
|-------------|-------------|-----|------------------|-----------------|--------------|-------------|------------------|---------------|
| 1           | 87          | F   | Moderate         | 110 mg twice daily | Spontaneous intra-parenchymal hemorrhage | 15          | 110              | 6              |
| 2           | 86          | M   | Moderate         | 110 mg twice daily | Traumatic multi-compartmental hemorrhage | 14          | 2                | 6              |
| 3           | 89          | M   | Normal           | 110 mg twice daily | Traumatic sub-dural hematoma | 15          | 163              | 6              |
| 4           | 72          | M   | Mild             | 150 mg twice daily | Spontaneous intra-parenchymal hemorrhage | 12          | 43               | 6              |
| 5           | 62          | M   | Mild             | 150 mg twice daily | Spontaneous intra-parenchymal hemorrhage | NA‡         | 30               | 5              |

*Kidney Disease Outcomes Quality Initiative chronic kidney disease criteria.
§Glasgow Coma Scale.
¶Time to drug was calculated as time from triage to drug in emergency department patients and time from symptom onset to drug in inpatients.
†Modified Rankin Scale: 1, no symptoms; 2, mild disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; 6, death.
‡Not available, patient was an inpatient and enrolment was delayed.

Table 1. Details of patients who received idarucizumab for dabigatran-associated intracranial hemorrhage.
idarucizumab. This raises questions on the therapeutic window for idarucizumab and whether with certain, extensive ICH its administration is futile.

**Limitations**

Although PTT is an imperfect measure of thrombin inhibition, it is widely available and correlates well with both plasma dabigatran concentration and dilute thrombin values in the therapeutic range [8]. All participating hospitals were referral centers which may have led to the disproportionate enrollment of sicker patients at risk for worse outcome. Conversely, the better outcomes reported in RE-VERSE AD may have been due to overrepresentation of patients with minor bleed or even artifactual ICH mimics on computed tomography. Our study design precludes assessment of patients who may have benefited from idarucizumab but did not receive it. Lastly, the small number of study subjects limits the generalizability of our findings.

**Conclusions**

Clinicians striving to provide high value care need specific criteria to determine when idarucizumab administration is likely to improve patient-centered outcomes after ICH. We believe it is judicious to rapidly administer idarucizumab to reverse dabigatran in ICH patients with a potential for neurological recovery. However, our results suggest that patients with dabigatran-associated extensive ICH do poorly despite reversal and that high quality care should not include the expensive administration of idarucizumab when it is unlikely to achieve previously stated goals of care.

**Acknowledgments**

We would like to thank Celine Dupont (McGill University Health Centre, Department of Pharmacy) for her invaluable support and technical input.

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