Characteristics, management and outcomes of adults with major trauma taking pre-injury warfarin in a Western Australian population from 2000 to 2005: a population-based cohort study

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ABSTRACT

Objectives: To describe the characteristics, management and outcomes of patients with major trauma who were taking warfarin; explore the use of rapid anticoagulation reversal; and assess the effect of reversal on outcomes.

Design and setting: Retrospective cohort analysis of prospective data extracted from the trauma registries and patient charts of the two adult trauma referral hospitals with neurosurgical units in Western Australia, 2000 to 2005. Inclusion criteria were: major trauma (injury severity score > 15); first international normalised ratio (INR) after injury > 1.4; and documented (in registry or chart) warfarin use.

Results: Eighty patients were identified. Their mean age was 76.8 years. Forty-six were men; 34 were transferred from another hospital; 28 died; and the functional outcomes of 58 were worse at discharge from hospital than before injury. Intracranial haemorrhage (ICH) occurred in 62, of whom 25 died; the difference in mortality between those with ICH and those without ICH was insignificant. Warfarin reversal started 17.4 hours (mean) after injury and the documented period between injury and completion of reversal was 54.2 hours (mean). Multiple logistic regression models, controlling for age, sex, on-scene Glasgow Coma Scale (GCS), initial INR and progressive ICH, showed no independent survival benefit for rapid reversal. Factors associated with mortality were age (22% increase per year [95% CI, 17%–34%]) and progressive ICH on computed tomography scan (24 of the 36 patients with progressive ICH died v one of the 26 patients with stable ICH died). Every point increase in on-scene GCS > 8 increased survival likelihood by 215% (95% CI, 119%–388%).

Conclusions: Patients with major trauma taking warfarin at the time of injury have high mortality rates, poor functional outcomes and long delays to initiation and completion of anticoagulation reversal. Rapid, appropriate warfarin reversal was rarely performed and was not independently associated with survival. Age, low on-scene GCS and progressive ICH were strongly associated with mortality, but presenting INR, ICH v no ICH, and sex were not.

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Trauma patients anticoagulated with warfarin are theoretically at risk of prolonged major bleeding. Studies of traumatic intracranial haemorrhage (ICH) suggest that patients taking anticoagulants have 2–6 times greater mortality.[1-3] Those without ICH may not have increased mortality but they may have longer, more complex admissions.[4-6] Patients taking anticoagulants seem to have no more traumatic ICH than age-matched controls, but bleeding, when it occurs, is more clinically apparent, with bleed size similar at presentation but with greater haematoma progression.[2,7,8] Progressive bleeding is associated with high mortality in patients with traumatic coagulopathic ICH (35%–85%), severely disabled survivors and worse outcomes for initially awake patients with "minor" head injuries.[2,7,9] Rapid, early warfarin reversal is recommended to improve outcomes.[4,5,7,9,10]

Authoritative guidelines strongly recommend rapid warfarin reversal for major bleeding, although there are few supportive prospective or randomised trial data.[11-13] Australasian guidelines recommend urgent reversal of international normalised ratio (INR) to < 5.0, with further actions correlated with clinical bleeding.[11] British and American guidelines suggest reversal of INR to < 2.0.[12,13] Vitamin K (intravenous), prothrombin complex concentrates (Prothrombinex-VF [PTX], CSL Bioplasma, Melbourne, Vic), or fresh frozen plasma (FFP) are recommended for warfarin reversal in Australia.[11]

Evidence shows that practice varies significantly from published guidelines. In Italian emergency departments, < 30% of patients with anticoagulant-associated traumatic ICH underwent reversal, and attempts were delayed.[2,14] One small prospective study of reversal effectiveness in anticoagulant-associated trauma ($n < 20$) suggested that rapid diagnosis and reversal reduced mortality from 48% to 10%.[9,14,15]

We were prompted to undertake this study by the observation, made by two of us (D M and V S) when reviewing trauma deaths, that patients taking warfarin had very poor outcomes and were over-represented among trauma deaths. It was also observed that warfarin reversal attempts were often delayed or ineffective. Our review of the literature, which found only a few small studies, suggested that our observations may not be unusual, but gave limited evidence for decision making and almost no Australasian data.[2,14,16]

We undertook an exploratory observational study of Australasian patients with major trauma who were taking warfarin. The aims of our study were to characterise the Western Australian major trauma population taking warfarin (2000–2005); describe warfarin reversal practice compared with guidelines; and study whether rapid reversal was associated with improved survival.

METHODS

Study design and population description

We analysed prospective trauma registry data from Western Australia's two neurosurgically capable hospitals for adults, which treat 90% of the state's major trauma patients (700–800 patients annually). The hospitals' registry entries for 2000–2005 (inclusive) were searched for major trauma patients (injury severity score [ISS] > 15) with first INR after injury > 1.4. Data on major trauma patients were used because warfarin reversal is not likely to be controversial in this group.

Patients were selected if their current warfarin use was documented either in the registries or hospital charts. Warfarin usage was not a required registry field but was likely to be documented by trauma coders. Registry data were transferred directly to Excel spreadsheets because the preservation of data integrity by Excel is well validated. We reviewed the charts of all potential study candidates for missed cases and additional data. Data points were defined before the chart review. Relevant computed tomogra-

phy (CT) reports (eg, reports of haematoma progression) and other results were accepted without review. Data from referring hospitals were gathered by onsite chart review, facsimile transfer or onsite clinician review and electronic communication. All data were de-identified and secured.

Statistical analysis

One of us (V S) extracted the required data from the two hospitals' medical records. To assess accuracy of the data extraction, another author (D M) reviewed 10 randomly selected records involving 541 data points. Inter-rater reliability was assessed using κ statistics. Descriptive analysis was undertaken for categorical and numerical data. Proportions and ranges were derived for categorical data. Means and medians were calculated for continuous data, and 95% confidence intervals were derived. Univariate analysis for initiation and completion of warfarin reversal (INR < 1.5) at < 2, < 4, < 12 and < 24 hours from injury was undertaken to assess association with survival. Logistic regression, with the Hosmer–Lemeshow goodness-of-fit test, was used to identify mortality predictors and control confounders. Results were expressed as odds ratios (ORs) with 95% confidence intervals. Data analysis was performed using SPSS version 15.0 (SPSS Inc, Chicago, Ill, USA).

Written institutional ethics approval was obtained for all involved sites.

RESULTS

The initial registry search yielded 436 patients with an ISS > 15 and INR > 1.4. Registry notation identified 77 patients taking warfarin at the time of injury, with one chart untraceable. Of the other 359 patients, 354 had charts available and, from these, four users of warfarin were identified, giving the study a final sample size of 80 patients. Extracted data had high accuracy with a κ of 0.76 (95% CI, 0.71–0.81) and 476/541 agreed data points (88%).

1 Demographic characteristics of the study sample ($n = 80$)

	Number of patients	Mean (95% CI)	Median (range)
Age (years)	80	76.8 (74.4–79.2)	79.0 (30.0–92.0)
Sex			
Men	46		
Women	34		
Presentation mode			
Direct	46		
Transferred	34		
Prehospital time (hours)*	80	14.5 (8.9–20.1)	4.0 (1.0–120.0)
Indications for warfarin			
AF or atrial flutter	35		
Prosthetic valve	17		
CVA	5		
AF + CVA	4		
DVT	4		
AF + prosthetic valve	3		
AF + TIA	2		
LV thrombus	2		
PE	2		
PE + thrombophilia	1		
DVT + PE	1		
LV thrombus + CVA	1		
DVT + AF	1		
PPM	1		
Unspecified	1		
Pre-injury ADL status			
Independent	51		
Partly dependent	26		
Fully dependent	3		
ISS	80	24.0 (21.9–26.1)	25.0 (16.0–75.0)
Scene GCS	80	12.7 (11.9–13.5)	14.5 (3.0–15.0)
Presence of ICH	62		
Initial INR	80	3.1 (2.8–3.4)	2.9 (1.6–10.0)

ADL = activities of daily living. AF = atrial fibrillation.
CVA = cerebrovascular accident. DVT = deep vein thrombosis.
GCS = Glasgow Coma Scale. ICH = intracranial haemorrhage.
INR = international normalised ratio. ISS = injury severity score.
LV = left ventricular. PE = pulmonary embolism.
PPM = permanent pacemaker. TIA = transient ischaemic attack.
* Time from injury to presentation at a study hospital. ◆

Population characteristics

The WA population in 2005 was about 2 million.[17] The estimated incidence of patients with major trauma taking warfarin and admitted to a trauma hospital was 0.7 per 100 000 population per year. The mean age of the study sample was 76.8 years; 46 patients were men, and 34 were transferred from another hospital. The mean time from injury to index site arrival was 14.5 hours. Warfarin was used predominantly to prevent complications from atrial arrhythmias or prosthetic heart valves. Pre-injury, 51 patients were independent. The mean ISS was 24.0; mean on-scene Glasgow Coma Scale (GCS) was 12.7; and 62 patients had ICH. Initial mean INR was 3.1. See Box 1.

Outcomes

Overall, 28 patients died and 12 were independent at hospital discharge. Functional status at discharge was worse than before injury for 58 patients. No differences in outcomes were seen between those with ICH and those without. In 36 of the 62 patients with ICH, bleeding progression, as shown on CT scans, strongly predicted death — of the 36 patients with progressive ICH, 24 died; of the 26 patients with stable ICH, one died ($P = 0.007$). See Box 2.

Warfarin reversal practices

Warfarin reversal was started in 66 patients. Documented reasons for not reversing anticoagulation included "patient stable", "CT stable", "INR low enough", "prosthetic valve present" and "patient unsalvageable". Reversal to INR < 1.5 did not occur in 15 of the 66 patients. The mean time from injury to the initiation of reversal was 17.4 hours, but for people who presented at the index hospitals it was 5.0 hours. The mean period from injury to documented reversal time (if achieved) was 54.2 hours (36.7 hours from initiation of reversal). See Box 3 and Box 4.

Many combinations of vitamin K, FFP and PTX were used in the 66 patients for whom warfarin reversal was initiated. A single agent was used in 17 patients (vitamin K for 10, FFP for seven); a combination of vitamin K and FFP was used in 30 patients; and recommended combinations of vitamin K, FFP

and PTX were used in eight patients (Box 5).[13] Platelets and cryoprecipitate were also used in some patients (but not to reverse warfarin). Two thromboembolic events occurred, both non-fatal: a deep vein thrombosis associated with a fractured leg, and a pulmonary embolus associated with protein S deficiency.

Initial doses of reversal agents are presented in Box 5. Two patients received oral vitamin K. Initial doses of vitamin K (median, 10 mg) were close to those recommended in guidelines (5–10 mg intravenously) but doses of other agents were often less than recommended doses, particularly PTX (median, 1.5 vials; approximately 10 IU/kg).

2 Morbidity and mortality outcomes of study sample

ADL outcome	Total patients ($n = 80$)	Patients with ICH ($n = 62$)
Independent	12	9
Partly dependent*	23	13
Fully dependent	16	14
Vegetative state	1	1
Dead	28	25
ADL same before and after injury	22	16
ADL worse after injury	58	46

ADL = activities of daily living. ICH = intracranial haemorrhage.
* Patients without head injury were more independent before injury but decline in status at hospital discharge was not significantly different for patients with ICH and those without. ◆

3 Warfarin reversal initiated, completed (INR < 1.5) and not completed for all patients v patients with intracranial haemorrhage (ICH)

Warfarin reversal	Total patients ($n = 80$)	Patients with ICH ($n = 62$)
Initiated	66	55
Completed	51	42
Not completed	15	13

INR = international normalised ratio. ◆

Effects of rapid warfarin reversal on mortality

Univariate analysis showed that initiating warfarin reversal at < 4 hours from injury was associated with a survival OR of 3.3 (95% CI, 1.1–10.0). The survival OR for patients with ICH was 6.9 (95% CI, 1.7–28.5). However, in multivariate logistic regression models, controlled for age, sex, on-scene GCS, initial INR and with or without progressive ICH, this effect disappeared.

Other predictors of outcomes

Logistic regression showed that age, on-scene GCS and progressive ICH significantly predict survival. Each year of age was associated with a 22% decrease in survival chance. Every on-scene GCS point > 8 increased survival odds by 215% (95% CI, 119%–388%). No patient with an on-scene GCS ⩽ 12 was independent by the time of discharge, and all with a GCS ⩽ 8 died. Progressive ICH decreased chance of survival by 96%. Sex, initial INR and reversal initiation or completion times did not predict survival.

DISCUSSION

Our study is among the largest published cohort studies of major trauma in patients taking warfarin. It is also among the largest to use data that are prospective and of consecutive patients from an isolated population. The observed demographic characteristics of the study sample — advanced age; nearly equal sex distribution; taking warfarin most commonly for atrial fibrillation and embolic disease; high prevalence of traumatic ICH; and mainly therapeutic INRs — are similar to most previous studies.[1,5,9,10,18] The estimated incidence of major trauma for patients taking warfarin in WA was low, at 0.7 per 100 000 population per year, but it is probably underestimated because the numbers of deaths on-scene, before transfer to hospital or where transfer was inappropriate, were not included in the data. Morbidity and mortality were high, even without ICH (unlike some reports).[4-6] The 35% mortality rate (28/80) is higher than that found in a previous study (9.4%), which included trauma of any severity.[4] The traumatic ICH mortality of 40% is comparable to that found in other studies (23%–85%).[1-5,9,10,18] The severe morbidity after traumatic ICH for patients taking warfarin is demonstrated by the functional status being worse at discharge than before injury in 74% of patients (although some might improve with rehabilitation); this finding is comparable to the 68.1% of patients with decreased function found in another study.[2] There were long delays from injury to initiating reversal (mean, 17.4 hours). The longest delays occurred at transferring hospitals, but there were still significant delays at trauma hospitals (5 hours). Delays were associated with late presentations, delayed transfers and slow initiation or lack of reversal agents at referring facilities. Although 5 hours between patient arrival and the start of reversal at a trauma hospital seems long, similar delays are reported for overseas tertiary centres.[2,9]

Our study did not show survival benefit for early initiation and completion of warfarin reversal on multivariate analysis, although it was present on univariate analysis. However, only 17 patients (13 with ICH) started reversal under 4 hours from injury and only eight (six with ICH) under 2 hours. Documented completion of reversal under 4 hours from injury was very rare and inadequate dosing regimens were common (Box 5). It has been suggested that initiating reversal under 2 hours may improve survival (from 10% to 48%) in traumatic ICH.[9] Another study documented that progressive bleeding mainly occurs under 6 hours from injury.[8] As only six patients with ICH started reversal under 2 hours in our study, a significant mortality reduction was unlikely

4 Time taken for warfarin reversal and administration of first dose of reversal agent after arrival at study hospitals for all patients v patients with intracranial haemorrhage (ICH)

Period	Warfarin reversal time (mean hours [95% CI])	
	All patients ($n = 80$)	Patients with ICH ($n = 62$)
Injury to initiation	17.4 (12.0–22.8)	19.0 (12.8–25.2)
Study hospital arrival to first dose	5.0 (3.2–6.8)	4.5 (3.3–5.7)
Injury to completion	54.2 (42.2–66.2)	55.8 (41.9–69.7)
Initiation to completion	36.7 (25.9–47.6)	35.6 (20.9–50.3)

5 Agents used for warfarin reversal, with number of patients for whom reversal was initiated and completed

Reversal agent*	Number of patients initiated (% [95% CI]) ($n = 66$)	Number of patients completed (% [95% CI]) ($n = 51$)
Vitamin K + FFP	30 (45% [33.4% to 57.5%])	25 (49% [13.7% to 62.7%])
Vitamin K only	10 (15% [6.5% to 23.8%])	7 (14% [4.3% to 23.2%])
FFP only	7 (11% [3.2% to 18.0%])	6 (12% [2.9% to 20.6%])
Vitamin K + FFP + PTX	8 (12% [4.0% to 20.0%])	5 (10% [1.6% to 18.0%])
Vitamin K + FFP + platelets†	4 (6% [0.3% to 11.8%])	4 (8% [0.5% to 15.2%])
Vitamin K + PTX	4 (6% [0.3% to 11.8%])	3 (6% [–0.6% to 12.3%])
FFP + PTX	1 (2% [–1.4% to 4.5%])	0
Vitamin K + FFP + Cryo†	1 (2% [–1.4% to 4.5%])	1 (2% [–1.8% to 5.8%])
Vitamin K + FFP + PTX + Cryo†	1 (2% [–1.4% to 4.5%])	0

Cryo = cryoprecipitate. FFP = fresh frozen plasma. PTX = Prothrombinex-VF.
* Initial doses of reversal agents (mean [95% CI]; median [range]): Vitamin K, 7.4 mg (6.6 to 8.2); 10.0 (0.5 to 10.0). FFP, 2.9 units (2.6 to 3.2); 2.0 (1.0 to 8.0). PTX, 1.5 vials or 750 IU (1.3 to 1.7); 1.5 (1.0 to 2.0).
† Platelets and Cryo not used as reversal agents. ◆

to be seen even if present. Reversal testing and documentation were probably delayed and, therefore, reversal for some patients was probably achieved more quickly than recorded. However, the lack of early repeat testing of INRs also reflects a non-urgent approach to reversal. The literature and guidelines are unclear about what constitutes rapid reversal.[11-13] We suggest early reversal should be defined as complete reversal by 4 hours from injury or 2 hours from hospital arrival. This needs to be investigated further.

Current Australasian guidelines recommend early reversal with combined therapy (including PTX) and continuous assessment until an INR < 5.0 is achieved and bleeding stops.[11] Use of the recommended regimen should achieve complete reversal in many patients. Unfortunately, the guidelines do not clearly deal with the more common situation of life-threatening bleeding with therapeutic INRs (the situation for approximately three-quarters of the patients in this study). The confusion around reversal decisions in this situation seems borne out by the major delays and inadequate interventions we found in our study. It would seem sensible to clarify and emphasise the need for urgent complete reversal in future updates of warfarin reversal guidelines.

Initial vitamin K doses were generally adequate (mean, 7.4 mg), although two patients had oral dosing.[11] Mean FFP dosing was 2.9 units (approximately 725 mL), but median dose was 2 units (eg, fewer than half of the patients had the recommended 3 units). Initial dosing of PTX (mean, 1.5 vials; approximately 10 IU/kg) was well below recommended doses (25–50 IU/kg)[11] and was used in only 13 patients. We do not have data on why PTX was used so infrequently. However, current guidelines were only formulated in 2004; anecdotally, advice from haematologists was variable and concerns about full reversal were commonly expressed because of perceived thromboembolic risks. Only eight patients had all three recommended reversal agents, but 47 had either FFP plus vitamin K or PTX plus vitamin K.[11] Although often slow and inadequate,[13-15] attempted reversal was more prevalent than that found in Italian emergency departments.[4] We did not assess clinicians' knowledge of reversal guidelines (or access to them), but it seems clear that implementation is patchy.

In our study, only two patients had thromboembolic events after reversal, substantially fewer than the number reported in another study (4/35).[18] However, anticoagulation was recommenced for many patients after they were deemed stable and, for a third, reversal was either incomplete or not initiated. Even so, the low rate of thromboembolic events in our study suggests if reversal is indicated it should not be avoided because of thromboembolic risk, and anticoagulation should be reinstated only when bleeding stops and if still indicated.[13-15]

Previous studies have suggested outcome predictors for patients with anticoagulant-associated traumatic ICH. Increasing age strongly predicts death and we found a 22% decrease in survival chance per year.[1,3,4] Similarly, GCS was strongly associated with survival, with each point increase about doubling survival odds.[4,12] Another study showed that 91.5% of patients with a presentation GCS < 8 died,[12] while we found that all patients with GCS < 8 died, suggesting low GCS may predict futility of treatment. Warfarin is strongly associated with traumatic ICH expansion, which probably mediates mortality.[10,11] Progressive bleeding decreased patients' survival chances profoundly. Twelve of the 36 patients with progressive bleeding had an initial GCS of 15, seven of whom died. Two of the seven patients who died did not undergo anticoagulation reversal, having been deemed neurologically stable until suddenly deteriorating. These data suggest that all patients with traumatic ICH and taking warfarin should be viewed as immediately life-threatened even when "stable". It has been suggested that high INRs increased mortality but we did not find this association, with 64 patients having therapeutic INRs.[3]

A limitation of our study was our need to use some retrospective data, although patient selection and most data were from prospective high-quality registries. A lack of agreed uniform criteria in this area of research meant we defined data differently from some studies. Despite being a relatively large series compared with previous studies, the study's overall numbers were small, so only very large clinical effects can be observed. We defined morbidity outcomes by functional status at hospital discharge because direct follow-up was made difficult by high expected mortality rates. Perth is an isolated city with distinctive regional problems, but the population is highly centralised, mainly metropolitan and has a mature system for trauma treatment. We used an INR of < 1.5 (rather than < 2.0) to define reversal because this is the level at which our neurosurgeons are willing to operate electively.

Further studies need larger populations, achievable either by expanding the study period (infeasible for prospective studies) or including more centres. Following up survivors at prespecified times to determine outcomes would allow better definition of medium-term dysfunction. Studies examining levels of knowledge among clinicians and availability of, and attitudes to, guidelines for anticoagulation reversal are required. Australasian guidelines should be more definitive about reversal and more

widely promulgated. Larger studies may confirm whether the initial GCS should inform decisions to withdraw therapy. Prospective interventional before-and-after studies would allow assessment and confirmation of the utility and feasibility of rapid reversal protocols. The findings of our study, combined with those of other recent studies, could guide the design of such trials.

The incidence of major trauma in those taking warfarin in WA is low, but morbidity and mortality among those taking warfarin who suffer major trauma are high. Increasing age, low GCS and progressive ICH strongly predict mortality. In our study, clinicians did not follow guidelines when faced with the possible need to reverse the effects of warfarin. Use of reversal agents was often delayed or not attempted (particularly at peripheral hospitals), and reversal was often completed slowly, with inadequate dosing and inappropriate combinations of agents. In particular, initial doses of PTX were well below recommendations.[13] Rapid initiation of warfarin reversal did not independently predict survival, but it was so rarely performed that potential survival benefits were unlikely to be seen.[15] Reversal was associated with a low rate of thromboembolic events. Further prospective investigation into compliance with guidelines and their clinical effectiveness is needed.

COMPETING INTERESTS

None identified.

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