A review of anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis

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Oral healthcare professionals must consider the possibility of uncontrolled bleeding when planning treatment for the client receiving anticoagulant therapy. One class of thrombolytic drugs, the vitamin K antagonist (e.g. coumarin, warfarin), is prescribed for many conditions associated with intravascular clotting and in 2007 in the United States warfarin was #17 in the top 200 most commonly prescribed drugs (1). The purpose of anticoagulation therapy is to reduce the risk of thrombosis and, at the same time, to provide a low risk for excessive bleeding events. The laboratory test used universally to determine efficacy and safety of vitamin K antagonists is the international normalized ratio (INR) which has replaced the prothrombin time as the measurement for determining dosage levels in this class of agents. The accepted therapeutic range has been established to be between two and three.

The study discussed in this paper is a pooling of data on studies that determined outcomes of various levels of INR with these agents. The authors distinguished four categories of INRs (<2, 2–3, 3–5 and >5). The combined outcome of thrombosis and bleeding in the various ranges of INR levels were determined. Findings from all studies included an absolute combined risk of thrombosis and bleeding of 10.6% (95% CI: 6.7–16.6) per year when the INR level is maintained at a ratio of <2. The common therapeutic ratio of between two and three had a combined risk of 4.3% (95% CI: 3.0–6.3). Levels between three and five had a combined risk of 7% (95% CI: 4.5–10.8) per year and an INR >5 had a dangerous combined risk of 52.3% (95% CI: 29.6–92.3). These data suggest that levels <2 or >5 pose a high risk for adverse outcomes. Physicians were advised to reconsider the conservative practice of keeping the INR <2. Numerous studies revealed that individuals spent more time with ratios below than above the therapeutic range. It was suggested this may be due to an overestimated risk of haemorrhage associated with oral anticoagulant use. It was also suggested that keeping the INR levels between three and four, as is the standard of care for individuals with prosthetic cardiac valves, carried a relatively low risk for excessive bleeding. Although researchers did not determine the combined risk for an INR level of between three and four, it is likely that the absolute risk would be lower than 7% per year (2).

This carefully performed meta-analysis of 19 studies provides evidence of serious risks of underdosing warfarin in order to keep the client at therapeutic levels. As well, the meta-analysis provides evidence that INRs slightly above three are not so dangerous as formerly thought. In individuals taking warfarin, INRs that are moderately higher than the therapeutic range of 2–3 are safer and more effective than subtherapeutic INR levels. The risk for thrombosis increased when INR levels were below two, however the risk of haemorrhage increased as the INR increased. The relative risk for haemorrhage at levels between three and five was 2.7 (1.8–3.9; $P < 0.01$) whereas the relative risk was 21.8 for INRs >5 (12.1–39.4; $P < 0.01$). Compared to the therapeutic range (INR 2–3), the risk of thromboembolism increased significantly when the INR was <2, and had a relative risk of 3.5 (2.8–4.4; $P < 0.01$). The authors conclude that the best strategy to minimize the risk of both haemorrhage and thromboembolic events is to keep patients within the therapeutic range (2–3), however when medical conditions exist that require more suppression of clotting factors, keeping the client at levels <5 are not so dangerous as was formerly thought. The literature supports providing minor oral surgery and similarly invasive oral procedures, such as periodontal debridement, when the INR is 3.5 or less (3, 4).

The authors identified limitations at the study level and at the review level. In terms of the study level, they suggested the possibility of bias in reporting the number of events since most of the studies failed to assign all events to ranges. In addition the person-years of observation at reported ranges may have been inaccurate. It was noted that the industry standard of reporting linear imputation of ratios between actual

measures has some error. It is likely that client INRs always vary linearly between actual measures. Two studies used imputation methods with error exceeding that of linear interpolation and two studies captured ratios that were measured outside of the study centre. There were limitations at the review level. The authors of the meta-analysis may have missed eligible studies despite an extensive literature search. In addition there was incomplete reporting of data in some studies that were included. Eight studies were not included since they did not report the number of adverse events and person-years of observation in discrete INR ranges. There was heterogeneity among the 19 studies included, however clustering of outcome data takes heterogeneity into account. Finally, as the study dealt with study-level variables, the meta-analysis had limited power to detect the influence of patient-level variables on the associations between anticoagulant intensity and risk of events.

In dental and dental hygiene practice settings, clinicians will encounter clients who are prescribed anticoagulant therapy. Therapy may be recommended for a variety of conditions including deep vein thrombosis, heart failure, arrhythmia, myocardial infarction, cerebrovascular accident and transient ischaemic attack. For these individuals, laboratory values for anticoagulant medication (INR) should be determined before oral procedures to determine the risks for uncontrolled bleeding. When the INR exceeds or is under the recommended values, oral procedures including scaling and debridement, should be delayed. This meta-analysis reported a strong and robust association between anticoagulation intensity and clinically relevant outcomes. Maximizing the length of time the client is kept within the therapeutic range of 2–3 should minimize the risk of both haemorrhagic and thromboembolytic events; however keeping INR levels between three and four is safer than keeping clients at levels <2.

References

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