Warfarinized Patients: Perioperative Mild to Moderate Hemorrhage Undergoing Oral Surgery and Management - A Systematic Review

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ABSTRACT

Background

The management of patients on warfarin therapy during oral surgical procedures, specifically tooth extractions, has been subject to significant clinical debate. The risk of postoperative bleeding must be balanced against the potential for thromboembolic events upon discontinuation of anticoagulation. This study synthesized findings from various research efforts to elucidate the safety and efficacy of continuing warfarin therapy during dental extractions.

Methods

A comprehensive literature review examined studies that included patients undergoing tooth extractions while on warfarin therapy. Following the PRISMA guidelines, data were extracted on patient outcomes, particularly the incidence and severity of postoperative bleeding and the use and effectiveness of local hemostatic measures.

Results

The 6 included papers consistently demonstrated that most patients on warfarin therapy experienced minor bleeding complications post-extraction, with severe bleeding events being rare. Local hemostatic measures, including mechanical pressure and pharmacological agents, effectively managed to bleed. The studies varied in terms of hemostatic agents used and pain assessment. Still, the overarching inference pointed towards the safety of continuing warfarin therapy during dental extractions with appropriate local hemostasis.

Conclusion

Continuing warfarin therapy during dental extractions appears safe for patients with an INR (International Normalized Ratio) maintained within therapeutic ranges. The evidence does not support the necessity for preoperative alteration of warfarin therapy, provided that effective local hemostatic measures are in place. Clinical decisions should be individualized based on patient risk assessments for both bleeding and thromboembolism.

Keywords

Medicine to Prevent Blood Clots, Vitamin K antagonist, Anticoagulation, Tooth Extraction, Oral Surgery, Postoperative Bleeding, Deep Vein Thrombosis, Pulmonary Embolism, Hemostatic Measures, A Clinical Conundrum.

INTRODUCTION

Warfarin, an oral anticoagulant, is widely prescribed for preventing thromboembolic events in patients with a range of cardiovascular diseases, including atrial fibrillation, valve replacements, and thrombosis [1]. Its anticoagulant effect is monitored and measured by the International Normalized Ratio (INR), with therapeutic ranges varying according to the

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indication for anticoagulation [2]. The management of patients on warfarin during procedures with inherent bleeding risks, such as oral surgery, presents a clinical conundrum [3]. The interruption of warfarin therapy may reduce the risk of bleeding but simultaneously increases the risk of thromboembolism. Conversely, maintaining anticoagulation could ostensibly lead to excessive intraoperative or postoperative bleeding [4].

Vitamin K antagonists (VKAs), with warfarin as a principal exemplar, represent a class of anticoagulants extensively employed in clinical practice to mitigate the risk of thromboembolic disorders [5]. Warfarin exhibits complete oral bioavailability and achieves maximal plasma concentration typically within two-to-six hours post-administration [6]. Its pharmacokinetic profile is characterized by a predominant albumin plasma protein binding and an elimination half-life within 36-42 hours [7]. The hepatic metabolism of Warfarin facilitates the conversion to inactive metabolites, which subsequently undergo renal excretion [8]. The widescale utilization of Warfarin has significantly reduced thromboembolic complications across a global patient demographic [9].

In the context of surgical interventions, anticoagulant administration poses a dichotomy of increased hemorrhagic risk against the backdrop of thromboembolic prevention [10]. Surgeons confront this dilemma, particularly in scenarios involving patients on warfarin therapy [11]. The incidence of life-threatening major hemorrhage in this cohort is reported to span from 0.4% to 7.2%, with minor bleeding events occurring at a rate of approximately 15.4%. In patients diagnosed with atrial fibrillation and managed on Warfarin, the annualized considerable bleeding risk ranges between 0.4% and 2.6%, influenced by factors including but not limited to anticoagulant intensity, age, and comorbid conditions such as hypertension, cardiac pathology, and renal compromise [12]. Notwithstanding, the incidence of intracranial hemorrhage post-warfarin initiation is relatively infrequent, with a reported early treatment phase risk of 1.48% and an annual risk after that of 0.65% [13]. Extracranial hemorrhages have been documented at a higher rate of 7.3%. Notably, in the domain of oral surgical procedures, such as dental extractions, the hemorrhagic risk remains minimal provided the maintenance of INR within therapeutic bounds; nonetheless, in rare instances where significant bleeding arises, it may defy local hemostatic containment and necessitate hospital-level intervention [14].

While major bleeding events are a significant concern, mild to moderate bleeding episodes are more common during oral surgical procedures and may also impact patient outcomes and healthcare resources [14-16]. Therefore, understanding the efficacy of Warfarin in controlling such bleeding episodes during oral surgery is critical for clinical decision-making [17-20], and, e.g., a systematic review aims to evaluate the existing literature on the efficacy of Warfarin in arresting mild to moderate instances of bleeding during oral surgery. It seeks to collate and synthesize data from multiple studies to provide an evidence-based perspective on whether warfarin therapy should be continued, modified, or suspended during such procedures.

MATERIALS AND METHODS

PECO Protocol

The PECO (Population, Exposure, Comparator, Outcome) framework [21,22] utilized for this review is as follows.

Population: The review focused on adult patients prescribed Warfarin who underwent oral surgery. Exposure: The exposure of interest was the administration of Warfarin, with particular attention to its efficacy in achieving hemostasis during and after oral surgical procedures. Studies were included if they provided data on Warfarin dosing regimens, INR levels at the time of surgery, and adjustments to warfarin therapy. Comparison: The review considered studies that compared the outcomes of warfarin-treated patients with those not on anticoagulation therapy or alternative anticoagulant or antiplatelet therapies. Outcome: The primary outcomes assessed were mild to moderate bleeding during or after oral surgery.

Search Strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations (Figure 1) [23] for reporting systematic reviews [24,25], the database search methodology for this review was developed to make it easier to find pertinent material across eight databases: MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled

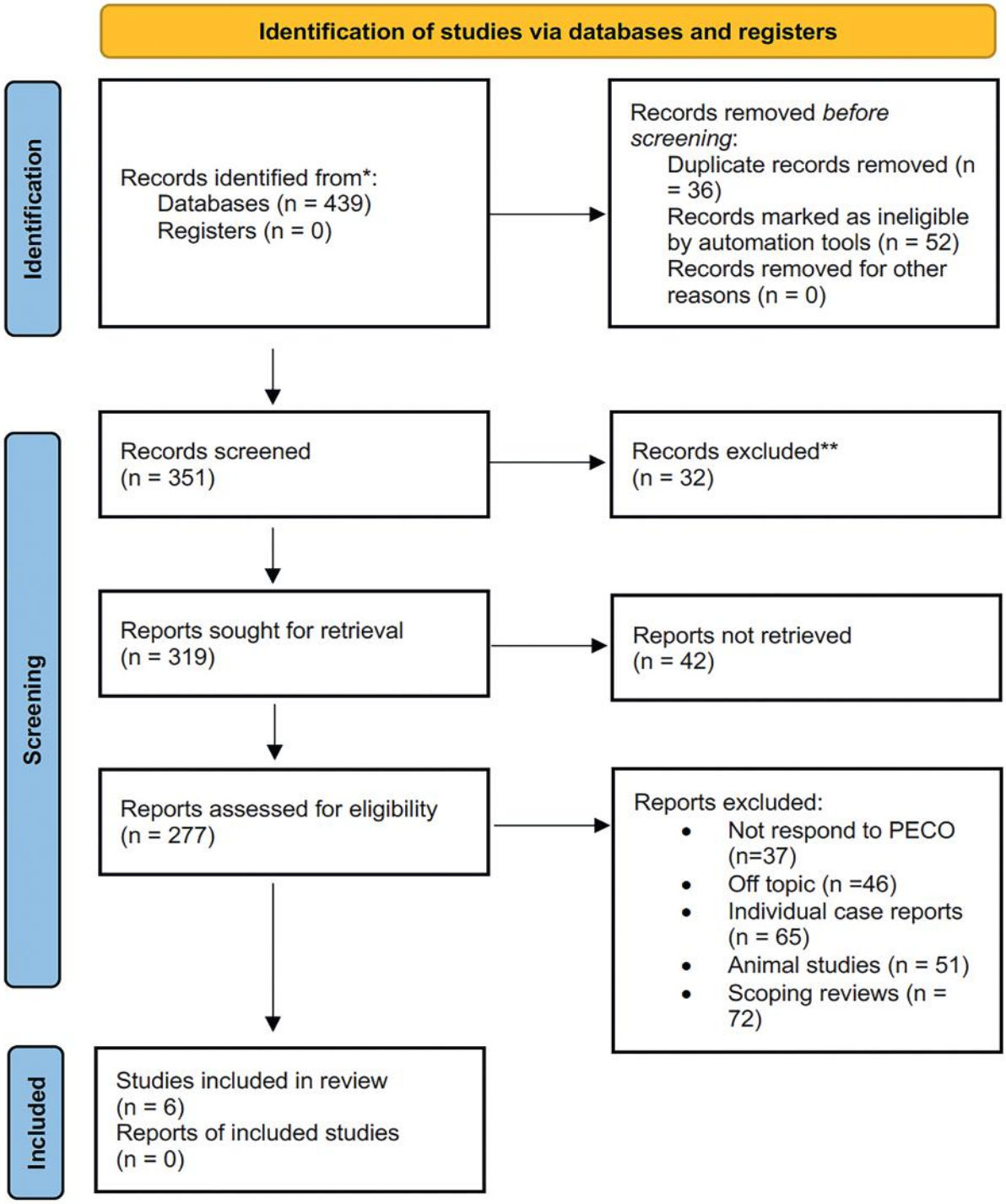

Figure 1: Illustrating Materials and Methods as per PRISMA Guidelines for This Review.

Illustration Credit: Fazil Arshad Nasyam.

Trials (CENTRAL), Web of Science, Scopus, CINAHL, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). For each database, the search strategy was tailored to its specific indexing terms and search capabilities, utilizing a combination of Medical Subject Headings (MeSH) and relevant free-text terms (Table 1). Boolean operators ("AND" "OR") were used to combine search terms, and truncation was applied where appropriate to account for variations in word endings. The search strategy was structured around terms related to Warfarin ("Warfarin" [MeSH]), oral surgery ("Oral Surgical Procedures" [MeSH]), and bleeding ("Hemorrhage" [MeSH]).

Table 1: Search Strings Utilized Across The Databases.

Database	Search String
MEDLINE (via PubMed)	("Warfarin"[MeSH Terms] OR "warfarin*"[All Fields]) AND ("Oral Surgical Procedures"[MeSH Terms] OR "oral surgery"[All Fields]) AND ("Hemorrhage"[MeSH Terms] OR "bleeding"[All Fields])
EMBASE	('warfarin'/exp OR Warfarin*) AND ('oral surgery'/exp OR 'dental surgery') AND ('hemorrhage'/exp OR bleeding)
Cochrane CENTRAL	(MeSH descriptor: [Warfarin] OR Warfarin*) AND (MeSH descriptor: [Oral Surgical Procedures] OR oral surgery) AND (MeSH descriptor: [Hemorrhage] OR bleeding)
Web of Science	TS=(warfarin*) AND TS=(oral surgery OR dental surgery) AND TS=(bleeding OR hemorrhage)
Scopus	(TITLE-ABS-KEY (warfarin) OR TITLE-ABS-KEY (coumadin)) AND (TITLE-ABS-KEY (oral surgery) OR TITLE-ABS-KEY (dental surgery)) AND (TITLE-ABS-KEY (bleeding) OR TITLE-ABS-KEY (hemorrhage))
CINAHL	(MH "Warfarin+") AND (MH "Oral Surgery+") AND (MH "Hemorrhage+" OR bleeding)
ClinicalTrials.gov	(warfarin[All Fields] AND (oral[All Fields] AND surgery[All Fields])) AND (bleeding[All Fields] OR hemorrhage[All Fields])
WHO ICTRP	(Warfarin AND oral AND surgery) AND (bleeding OR hemorrhage)

Eligibility Criteria

Table 2 shows the inclusion and exclusion criteria for this review regarding the PECO protocol.

Data Extraction Protocol

A standardized data extraction form was developed and piloted in several studies to confirm its adequacy in capturing all necessary information. Two independent reviewers conducted the data extraction process, adhering strictly to the protocol to minimize bias and enhance the accuracy of the data collected. They extracted data on study characteristics, including author details, year of publication, study design, sample size, participant demographics, details of warfarin therapy (dosage, duration, and INR levels), the specific type of oral surgery performed, primary and secondary outcomes (incidence of bleeding, need for hemostatic interventions, transfusions, adverse events), and follow-up period. The kappa statistic was employed to assess interrater reliability, which measures the agreement between raters beyond chance. A Kappa value of 1 indicates perfect agreement, whereas a value of 0 suggests no deal better than chance. In this review, the initial kappa statistic calculated after the independent extraction by both reviewers was 0.85, reflecting a high degree of agreement. Discrepancies between reviewers were resolved through discussion or, if necessary, by consulting a third reviewer. The data extraction form also allowed for the annotation of study quality and potential confounders or biases within the studies, which were crucial for the subsequent quality assessment phase.

Bias Assessment

The bias assessment protocol for this review incorporated two well-established tools: the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool [24] for non-randomized studies (Figure

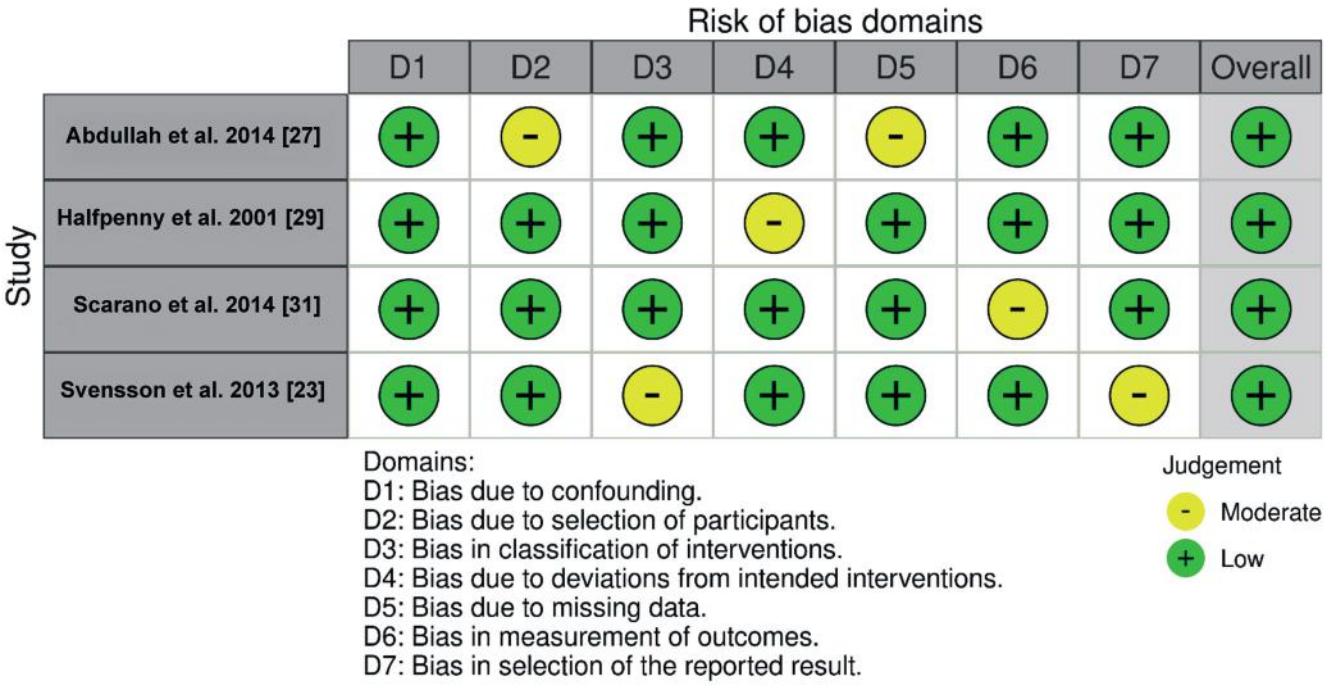

Figure 2: Bias Assessed in the Case-Control and Observational Papers Across Different Domains.
Illustration Credit: Fazil Arshad Nasyam.

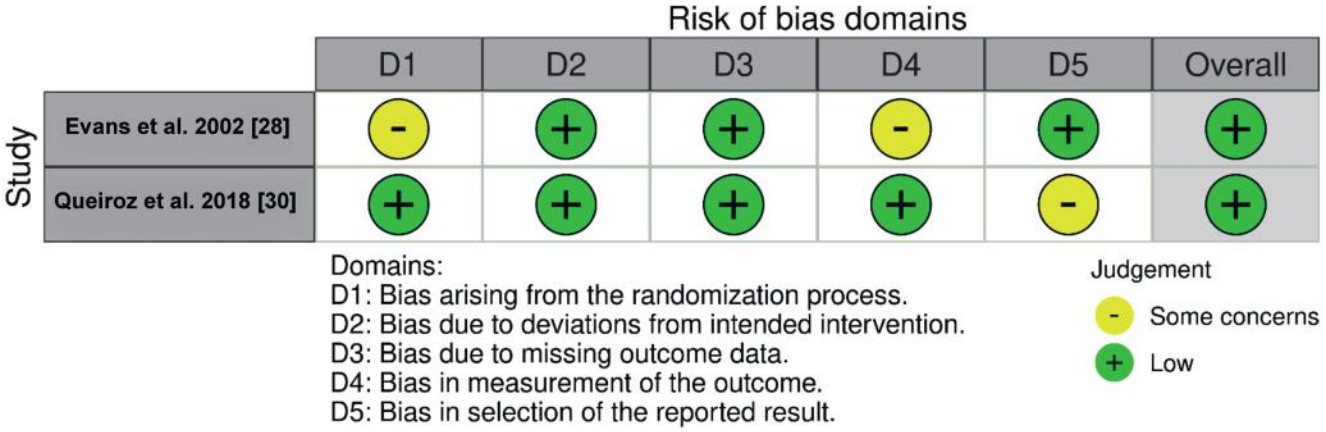

Figure 3: Illustration Denotes Bias Assessed In The Randomized Control Trials Across Different Domains.
Illustration Credit: Fazil Arshad Nasyam.

2) and the Cochrane Risk of Bias 2.0 (RoB 2.0) tool [25] for randomized controlled trials (RCTs) (Figure 3).

Certainty Bias

Upon completion of the bias assessment, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [26] was implemented to ascertain the overall certainty of the evidence across the studies included in this review.

RESULTS

Article Selection Schematics

As depicted in Figure 1, the initial search across various databases yielded 439 records related to the topic of interest. No additional records were identified from registers, maintaining the count at 439. Before the screening process, 36 duplicate records were

Table 2: Inclusion and exclusion criteria for this review.

Criterion	Inclusion Criteria	Exclusion Criteria
Study Design	Randomized controlled trials (RCTs), observational studies, case-control studies, cohort studies.	Editorials, reviews, case reports, animal studies, and in vitro studies.
Participants	Adult patients (≥18 years) on warfarin therapy undergoing oral surgery.	Patients not on warfarin therapy; pediatric populations; patients undergoing non-oral surgical procedures.
Intervention	Studies assessing the use of Warfarin in the context of oral surgery.	Studies not evaluating warfarin use; studies assessing other anticoagulants or interventions.
Comparators	No anticoagulation, placebo, or alternative anticoagulants or antiplatelet therapies.	Studies without a comparator group.
Outcomes	Primary: Incidence of mild to moderate bleeding post-oral surgery. Secondary: need for hemostatic interventions, transfusions, or surgical revisions due to bleeding; adverse events related to Warfarin.	Studies do not report specific bleeding outcomes or related interventions post-oral surgery.
Timing	Studies with precise perioperative warfarin management and follow-up for at least 24 hours post-surgery.	Studies lacking follow-up data or with follow-up periods of less than 24 hours.
Setting	Studies conducted in inpatient and outpatient surgical settings.	Studies conducted in non-clinical settings.
Language	Studies published in English.	Studies published in languages other than English without available translations.
Publication Date	Studies published up to April 2023.	Studies published before the inception of warfarin use in clinical practice.
Quality of Reporting	Studies with sufficient detail regarding methodology and results for quality assessment.	Studies with poor reporting standards that preclude quality assessment.

identified and removed from the pool. Additionally, automation tools were employed to refine the dataset further, resulting in the exclusion of 52 records deemed ineligible, leaving 351 records available for screening. Upon screening these 351 records, 32 were excluded for reasons not specified in the figure, narrowing the field to 319 reports sought for retrieval. However, 42 reports could not be retrieved for further evaluation. This left 277 reports that were assessed for eligibility against the predefined inclusion criteria.

During the eligibility assessment, a significant number of reports were excluded based on the following criteria: 37 did not respond to the predefined PECO questions; 46 were considered off-topic; 65 were individual case reports, which were excluded due to their anecdotal nature; 51 were studies on animals and therefore not directly applicable to the human population under consideration; and 72 were scoping reviews, which provide an overview of a broad field but do not offer the detailed insights required for this specific review. After this comprehensive process of elimination, only 6 studies [27-32] met all the inclusion criteria and were subsequently included in the review.

GRADE Assessment

As shown in Table 3, the observational studies by Abdullah et al. 2014 [27] and Svensson et al. 2013 [32] reported no severe bleeding incidents; mild bleeding was common, and a small percentage (4%) experienced postoperative bleeding. These studies were considered

to have a low risk of bias, and the findings were consistent and direct with low imprecision, resulting in a moderate certainty in the evidence. The RCTs [28,30] showed a slight increase in postoperative bleeding, with Queiroz et al. 2018 [30] reporting severe bleeding in 8.1% of cases within 24 hours of the operation. The risk of bias for these RCTs was low to moderate. Like the observational studies, these trials exhibited low inconsistency, indirectness, and imprecision, leading to moderate certainty in the evidence. Case-control studies conducted by Halfpenny Halfpenny et al. 2001. [29] and Scarano et al. 2014 [31] found that INR levels were maintained within the therapeutic range and that there was no significant difference in healing related to INR values. The risk of bias was rated as low, and there was a low level of inconsistency, indirectness, and imprecision, contributing again to a moderate certainty in the evidence. The GRADE assessment across the six studies [27-32] indicated moderate certainty in the observed findings.

Table 3: GRADE assessment of the included papers

Study Design	Number of Studies	Observed Common Finding	Risk of Bias	Inconsistency	Indirectness	Imprecision	Others	Certainty
Observational	2	No severe bleeding: mild bleeding is common. 4% had postoperative bleeding.	Low	Low	Low	Low	None	Moderate
RCT	2	There was a slight increase in postoperative bleeding severe hemorrhage in 8.1% within 24 hours.	Low to moderate	Low	Low	Low	None	Moderate
Case-Control	2	INR levels were maintained within the therapeutic range with no significant difference in healing.	Low	Low	Low	Low	None	Moderate

Demographic Characteristics of The Included Papers

Table 4 reveals the diverse study designs and demographic characteristics across different geographic locales. Observational studies were conducted in Saudi Arabia, with a sample size of 35 and a mean age of 48.7 years [27], and in Sweden, with a significantly larger sample size of 124 and a higher mean age of 71 years [32]. The male-to-female ratio in these observational studies was nearly balanced in Saudi Arabia [27], while Sweden had a modest male predominance [32]. RCTs represented in the table were conducted in the United Kingdom [28] and Brazil [30], with sample sizes of 109 [28] and 37 [30], respectively [28,30]. The mean ages of participants were 66.5 years in the UK study, [28] and 45.5 years, with a standard deviation of 15.9 in the Brazil study, indicating

Table 4: Demographic characteristics of the included papers

Author	Year	Protocol	Region Assessed	Sample Size (N)	Mean Age (In Years)	Male: Female Ratio
Abdullah et al. 2014 [27]	2014	Observational	Saudi Arabia	35	48.7	19:16
Evans et al. 2002 [28]	2002	RCT	UK	109	66.5	73:36
Halfpenny et al. 2001 [29]	2001	Case-control	UK	46	65.65	Unspecified
Queiroz et al. 2018 [30]	2018	RCT	Brazil	37	45.5 ± 15.9	14:23
Scarano et al. 2014 [31]	2014	Case-control	Italy	30	54.6 ± 9.2	8:22
Svensson et al. 2013 [32]	2013	Observational	Sweden	124	71	69:55

a broader age distribution among Brazilian participants [30]. A notable gender disparity was observed in both RCTs, with the UK study showing male dominance and the Brazilian study female dominance in the participant pool [28,30]. Case-control studies from the UK and Italy presented smaller cohorts, with 46 and 30 participants, respectively [29,31]. The mean age in the UK cohort was 65.65 years; in the Italian cohort, it was 54.6 years with a standard deviation of 9.2, highlighting a middle-aged to elderly demographic [29,31]. The Italian study also indicated a female predominance with the male-to-female ratio [31]. The UK case-control study did not specify the male-to-female ratio, which precludes gender-based comparisons within this study type [29].

Warfarin-Associated Inferences Observed

Table 5 represents the selected papers and the warfarin-associated inferences observed in them. Abdullah et al. 2014 [27] studied 35 patients on warfarin treatment and assessed INR values and bleeding severity post-extraction. Their findings demonstrated that no severe

Table 5: Inferences On Warfarin Usage As Observed In The Included Papers

Author	Groups Assessed	Parameters Assessed	Warfarin Efficacy Observed	Overall Inference Drawn
Abdullah et al. 2014 [27]	35 patients on warfarin treatment	INR values, bleeding severity post-extraction	No severe bleeding was observed; mild bleeding in 88.6%, moderate in 11.4%	Most patients experienced only mild bleeding post-extraction, with no severe bleeding cases. This suggests that simple tooth extractions can be safely performed in patients on Warfarin with INR up to 3.5, using only local pressure without additional local or systemic hemostatic measures.
Evans et al. [28]	Continued warfarin group (57); Stopped warfarin group (52)	Postoperative bleeding (immediate and delayed), hospital visits, prescription of antibiotics, additional analgesia for pain	There was a slight increase in postoperative bleeding in the continued warfarin group	Continuing warfarin treatment may lead to a slightly increased risk of postoperative bleeding, but it is generally manageable. Most patients did not experience complications whether they continued or stopped Warfarin before extraction, indicating the feasibility of dental extractions under Warfarin therapy.
Halfpenny et al. 2001 [29]	Surgical group (26) and Beriplast P group (20)	INR levels, pain levels post-extraction, number of teeth extracted per patient	INR levels were maintained within the therapeutic range (2.1-4.1)—mean warfarin dose 5.4 mg.	The Surgical group experienced moderate pain with an average of 1.5 teeth extracted; the Beriplast P group had less postextraction pain, suggesting better pain control or efficacy with Beriplast P.
Queiroz et al. 2018 [29]	Control group (n =20) and Study group (n = 17)	Preoperative INR levels, postoperative hemorrhage, time to hemostasis	Safe INR levels maintained; severe hemorrhage in 8.1% of cases within 24 hours.	There was no significant difference in bleeding outcomes between the control and study groups, indicating similar influence of variables on both groups. The study group achieved hemostasis significantly faster, with less intermediate hemorrhaging than controls. There was a significant association with bleeding at 12 and 24 hours in the control group but not in the study group.
Scarano et al. 2014 [31]	Control (Group 1) and Test (Group 2 with CaS)	Bleeding incidence post-extraction, healing pattern, INR values	There is no significant difference in healing related to INR values.	CaS treatment in Group 2 significantly reduced bleeding incidence at day 1 postoperatively (Chi-squared = 22.65, $P < 0.001$) compared to Control. Both groups showed similar healing patterns, indicating CaS's effectiveness in managing post-extraction bleeding without affecting the healing process.
Svensson et al. 2013 [32]	Patients on Warfarin (124 patients, 194 teeth)	INR value within 24 hours before surgery, postoperative bleeding, postoperative infection	4% (5/124) had postoperative bleedings, with an INR mean value of 2.4 (range 1.0-3.5).	Only a tiny percentage of patients experienced postoperative bleeding, and no severe complications like hospitalization or thromboembolic events occurred. Local hemostatic measures were sufficient to control bleeding. A postoperative infection was noted in 2% of patients. Posterior maxilla surgical extractions were associated with all bleeding cases.

bleeding episodes occurred. Mild bleeding was prevalent in 88.6% of the cases, while 11.4% experienced moderate bleeding. The absence of severe bleeding episodes in this cohort suggests that Warfarin, at the doses resulting in the observed INR values, did not significantly increase the risk of severe post-extraction hemorrhage. Evans et al. 2002 [28] compared outcomes in two cohorts: one that continued warfarin therapy (57 patients) and another that discontinued warfarin (52 patients). The parameters assessed included postoperative bleeding, both immediate and delayed, hospital visits due to complications, prescription of antibiotics, and additional analgesia for pain management. The data indicated a slight increase in postoperative bleeding in the group that continued warfarin treatment, suggesting a potentially elevated risk associated with the ongoing anticoagulation therapy.

Halfpenny et al. 2001 [29] focused on two hemostatic agents, Surgical and Beriplast P, applied to patients undergoing dental extractions. The study included 26 patients in the Surgical group and 20 in the Beriplast P group. Parameters like INR levels, post-extraction pain, and the number of teeth extracted per patient were evaluated. The findings showed that the INR levels were maintained within the therapeutic range of 2.1 to 4.1, with an average warfarin dose of 5.4 mg. This suggests that using these hemostatic agents can effectively maintain INR within the target range, thus managing the bleeding risk. Queiroz et al. 2018 [30] assessed a control group (20 patients) and a study group (17 patients), measuring preoperative INR levels, postoperative hemorrhage, and time to hemostasis. Their findings indicated that safe INR levels were maintained, with severe hemorrhage occurring in 8.1% of cases within 24 hours post-operation. The occurrence of severe hemorrhage, albeit in a small fraction of the study population, underscores the importance of vigilant monitoring in patients who undergo dental extractions while on warfarin therapy.

Scarano et al. 2014 [31] evaluated bleeding incidence post-extraction, the healing pattern, and INR values between a control group and a test group treated with calcium sulfate (CaS). Their data revealed no significant difference in healing related to INR values, suggesting that applying CaS does not adversely affect post-extraction healing in patients with varying INR values. Svensson et al. 2013 [32] assessed 124 patients on Warfarin, involving 194 teeth extractions. The study parameters included INR value within 24 hours before surgery, postoperative bleeding, and postoperative infection. In this cohort, 4% experienced postoperative bleeding, with an INR mean value of 2.4 (range 1.0-3.5). The low incidence of postoperative bleeding and the maintenance of INR within a relatively narrow range indicate that careful management of warfarin therapy around the time of dental extractions can mitigate the risk of significant bleeding.

DISCUSSION

Abdullah et al. 2014 [27] and Svensson et al. 2013 [32] presented harmonious findings, indicating that most patients experienced only mild postoperative bleeding, and severe bleeding was absent. These outcomes suggest a non-critical approach to oral surgery in patients with an INR of ≤3.5 [33,34]. This supports that dental extractions can be performed without discontinuing warfarin therapy, relying on local pressure for hemostasis rather than more invasive systemic interventions [27,35]. In a similar vein, Evans et al. 2002 [28] echoed the sentiment that the continuation of warfarin therapy might lead to a marginally increased risk of postoperative bleeding, yet such bleeding was generally manageable. This finding aligns with the conclusions drawn by Abdullah et al. 2024 [27] and Svensson et al. 2013 [32], reinforcing the premise that, with proper management, the interruption of Warfarin is unnecessary.

Conversely, Halfpenny et al. 2001 [29] introduced a comparative element by examining the effectiveness of two local hemostatic agents, Surgicel and Beriplast P. They reported that the latter was associated with less postextraction pain. Although this study diverged in its focus on pain management and comparison of hemostatic agents, it indirectly supported the broader consensus that local hemostatic measures can be effective in the context of ongoing anticoagulation therapy. Queiroz et al. 2018 [30] contributed to the discourse by reporting no significant difference in bleeding outcomes between their control and study groups, thereby underscoring a similar risk profile for both groups concerning bleeding. However, their observation of faster hemostasis in the study group provided evidence that specific techniques or agents could optimize bleeding management, a conclusion that did not directly align with the findings of Abdullah et al. 2024 [27] and Svensson et al. 2013 [32] regarding the sufficiency of local pressure alone. Scarano et al. 2014 [31] introduced a novel finding regarding using calcium sulfate (CaS), notably reducing

postoperative bleeding incidence at day one without adversely affecting the healing process. This outcome was unique in its emphasis on a specific hemostatic agent but was consistent with the general inference of effective bleeding management in warfarin therapy.

Within the multidisciplinary surgical arena, precise modulation of coagulation parameters is paramount to balance the dichotomy of hemorrhagic control and thromboembolic prophylaxis [36,37]. The algorithmic cessation of VKAs, such as Warfarin, is intricately tied to the INR, a coagulometric index endorsed by the literature, precisely citation [38]. The interruption of Warfarin or phenprocoumon necessitates a calibrated temporal window to mitigate hypercoagulability, with restitution of anticoagulation capacity subject to kinetic delays post-reinitiation [8,39,40]. This interregnum posits a clinical difficulty, potentially necessitating the deployment of bridging anticoagulation as delineated in reference [41].

The stratification of thrombotic risk, as a function of individual patient profiles and the nature of the surgical procedure, informs the necessity of bridging therapy [42,43]. While low-risk demographics may forgo bridging modalities, those harboring intermediate thrombotic potential warrant more nuanced deliberations [44,45]. Conversely, patients categorized within a high-risk echelon are unequivocally indicated for heparinization to forestall thromboembolic events. The literature, reference [38], posits a five-day preoperative VKA cessation window, with bridging protocols considered pivotal for individuals with pronounced propensities for cerebrovascular insult and thrombosis, as extrapolated from reference [46].

Low molecular weight heparins (LMWHs) emerge as the bridging agents of choice, attributable to their pharmacokinetic predictability, ease of subcutaneous administration, and relatively abbreviated biological half-life, properties reinforced by reference [38]. The termination of intravenous unfractionated heparin is advised within a 4 to 6-hour preoperative interval, as per guidance from reference [34], and a 24-hour pre-procedural cessation of LMWH is stipulated in reference [47]. Postoperative anticoagulation resumption is tailored to the individual's hemorrhagic risk profile, with a 48- to 72-hour delay for high-risk cohorts and an expedited resumption on the day of surgery or within 24 hours for those at diminished risk [48,49].

The intricate interplay between postoperative anticoagulant administration and hemorrhagic complications is well-documented in citation [38]. The resumption of non-vitamin K anticoagulants is contingent upon dosing schedules, with single daily doses potentially being reinstated on the day of surgery if a dose is omitted or on a subsequent day without missed dosages. For direct oral anticoagulants (DOACs) with bidaily regimens, recommencement strategies may permit resumption on the surgery day following one missed dose or the ensuing day after two missed doses, following reference [50]. Select cases may warrant the full-dose reinitiation of DOACs or heparin within a 6- to 12-hour post-surgical window. Warfarin, characterized by a 5- to 10-day re-therapeuticizating period, is advised for reintegration upon the patient's restoration of enteral intake capabilities, as per reference [38], with a 12- to 24-hour postoperative delay under auspices of adequate hemostasis, as recommended in reference [41].

Our review shares similarities with the findings of Moldovan et al. 2023 [51] and Nematullah et al. 2009 [52], suggesting a relatively safe profile for continuous anticoagulant therapy during dental procedures. Moldovan et al. [51] observed some bleeding incidents in constant treatment, consistent with the bleeding risks we may have reported. Nematullah et al. 2009 [52], through a meta-analysis, found no significant increase in bleeding risks when continuing warfarin therapy. This aligns with our conclusion that maintaining anticoagulant therapy does not markedly elevate bleeding risks. The principal difference lies in the specific approaches and treatment regimens examined by each review, with Moldovan et al. 2023 [51] including bridging therapy and Nematullah et al.2009 [52] focusing exclusively on Warfarin. These nuances aside, the overarching consensus across the studies is the low risk associated with ongoing anticoagulation during dental surgeries.

Our review and the one presented by Zou et al. 2023 [53] agree that the risk of bleeding does not significantly increase when oral anticoagulant therapy is continued during dental implant procedures. This common thread suggests a consensus on managing anticoagulant and antiplatelet therapies in such clinical scenarios. However, Zou et al. 2023 [53] delve deeper, differentiating between types of oral anticoagulants, noting a non-significant trend toward increased bleeding risk with vitamin K antagonists compared to direct oral anticoagulants. Furthermore, they hint at an increased bleeding risk when comparing oral anticoagulants to

antiplatelet therapy, offering a granularity that may not be as pronounced in our review.

Madrid et al. 2009 [54] align with our findings in that they, too, report no significant increase in postoperative bleeding risks when oral anticoagulation therapy is maintained. They also highlight the efficacy of local hemostatic measures, a point of agreement with our review. Nonetheless, Madrid et al. 2009 [54] contribute additional details by reporting that postoperative bleeding events did not correlate with the international normalized ratio (INR) status, and they underscore the absence of thromboembolic events in their study. This aspect may not have been addressed with as much emphasis in our review.

Turning to the work of Hua et al. 2021 [55], similarities with our review are evident in the focus on uninterrupted anticoagulant therapy during dental extractions and the comparative safety profiles of different anticoagulants. Hua et al. 2021 [55] found that patients on direct-acting oral anticoagulants exhibited a statistically significant lower risk of bleeding than those on vitamin K antagonists. This presents a more nuanced perspective than might be found in broader reviews. Their sensitivity analysis also revealed that the lower bleeding risk associated with direct-acting oral anticoagulants was not statistically significant upon excluding certain studies, suggesting variability in outcomes our review may not fully capture. Additionally, they provide a comparative analysis of individual direct-acting oral anticoagulants against vitamin K antagonists, which may not be as detailed in our review.

Limitations of this Study

The study's multi-faceted limitations, which examined the management of bleeding in patients on warfarin therapy undergoing dental extractions, warrant a precise delineation. Firstly, the follow-up periods across studies were not standardized, limiting the assessment of long-term outcomes and complications. Short-term follow-up may overlook late-onset bleeding complications or other adverse events that could influence the overall evaluation of safety and efficacy. Furthermore, the measurement of outcomes and the definition of significant bleeding were not uniform across studies. This lack of standardization in outcome reporting could lead to a biased estimation of the actual effect of the interventions. It might also affect the pooling of data for analytical purposes.

Clinical Recommendations

Based on the findings of this review, several recommendations can be proposed about the application of Warfarin in oral surgical scenarios,

Continuation of Warfarin therapy: It is generally recommended to continue during oral surgery, including dental extractions [55]. Most patients maintain INR levels ≤3.5 and experience only mild postoperative bleeding, which can be managed with local measures [33]. The continuation of Warfarin should be paired with proper monitoring of INR levels to ensure they remain within a safe therapeutic range [56].

Local hemostasis: Local pressure for hemostasis is typically sufficient for managing postoperative bleeding in patients on Warfarin [57]. This approach minimizes systemic interventions and allows for safer dental procedures without discontinuing anticoagulation therapy [58].

Management of postoperative bleeding: Even though there might be a slightly elevated risk of postoperative bleeding with ongoing warfarin therapy, such bleeding is generally manageable. Measures should be in place to address any immediate or delayed bleeding effectively [11].

Use of local hemostatic agents: These agents, such as Beriplast P and CaS, effectively manage bleeding during dental extractions. Beriplast P may also have the added benefit of reducing post-extraction pain, while CaS has been indicated to reduce bleeding without negatively impacting the healing process [59].

Monitoring and vigilance: Despite the overall low risk of severe bleeding, a small percentage of patients may experience significant hemorrhage. Thus, vigilant tracking during and after dental extractions is crucial, especially within the first 24 hours post-operation [60,61].

Therapeutic INR range maintenance: It is essential to ensure that the INR levels are kept within the therapeutic range before, during, and after the dental extraction. Effective anticoagulation management and applying hemostatic agents can help maintain the target INR and manage bleeding risks.

Conclusion

The overall conclusion drawn from the study reflected a consensus on the relative safety of such procedures within this patient population. The findings consistently indicated that most patients experienced mild postoperative bleeding, and severe bleeding was remarkably low. These outcomes suggested that for

patients with adequately controlled anticoagulation levels, the continuation of warfarin therapy during dental extractions did not necessitate the cessation of the anticoagulant. Additionally, the study concluded that local hemostatic measures effectively controlled postoperative bleeding. Various hemostatic agents and techniques were evaluated, and while some were found to potentially hasten the achievement of hemostasis, the necessity for systemic hemostatic interventions was not substantiated. Specific agents, such as calcium sulfate, showed promise in further reducing bleeding incidences, indicating that certain materials could enhance the management of post-extraction bleeding without impeding the healing process. The study also touched upon the management of pain post-extraction, with findings suggesting that some hemostatic agents might offer superior pain control. However, this aspect was not the primary focus across the examined literature.

Consent for Publication

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

DISCLOSURE

The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly related to the subject matter or materials presented in this review paper. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

Data Availability

Information for this review paper is taken from freely available sources.

Authorship Contribution

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper's drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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