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Review

Hemostatic Agents for the Management of Bleeding Risk Associated with Oral Anticoagulant Therapy Following Tooth Extraction: A Systematic Review

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Abstract: The occurrence of bleeding following dental extraction is a relatively common complication. A history of therapy with oral anticoagulants represents a major favoring factor, both in patients treated with vitamin K-antagonists (especially warfarin) and with direct oral anticoagulants (DOACs). Several local hemostatic measures can be applied to limit the bleeding risk in these patients. The aim of this systematic review is to evaluate what measures can be adopted to limit the bleeding risk following dental extractions in patients treated with oral anticoagulants. A literature search was performed, and 116 articles were retrieved. Titles and abstract analyses excluded 91 articles, and three more articles were excluded following full-text analysis. The systematic review was performed on 22 articles. Among the included articles, 20 studies reported on patients treated with warfarin, and two studies on patients treated with DOACs. The agents employed included local intra-alveolar agents, tranexamic acid, and PRF. The included studies were all at moderate/high risk of bias. Moreover, limited evidence is available on hemostasis in patients treated with DOACs. The available evidence hinders stating the superiority of one agent over the others. Further research is advised to increase the level of evidence of the application of hemostatic agents in patients treated with oral anticoagulants.

Keywords: surgery; oral; tooth extraction/adverse effects; oral hemorrhage/etiology; oral hemorrhage/prevention & control; coumarins; direct factor Xa inhibitors; direct oral anticoagulants

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1. Introduction

Dental extractions are the most common procedures performed in routine dental practice. Bleeding and oozing from the surgical wound are frequently encountered, and mostly self-limiting, complications [1]. However, in patients treated with vitamin K antagonists or direct oral anticoagulants (DOACs), additional measures may be required to manage and limit the risk of post-operative bleeding [1].

Vitamin K antagonists include coumarin and its derivatives such as warfarin. Their mechanism of action is based on the inhibition of prothrombin and clotting factors formation. Dose adjustments are often required in order to maintain the target International Normalized Ratio (INR) of 2.5 (therapeutic range 2–3) [2]. To date, warfarin is the most prescribed oral anticoagulant for the management of thromboembolic disorders, despite its narrow therapeutic index and the high variability in clinical response [3,4].

DOACs have been introduced in recent years for the management of several cardiovascular conditions, including treatment of venous thromboembolism, stroke prevention in non-valvular atrial fibrillation, and for thromboprophylaxis following orthopedic surgery [5]. The DOACs category includes four anticoagulants which directly inhibit the coagulation cascade. Dabigatran is a direct thrombin inhibitor, while apixaban, rivaroxaban, and edoxaban exert their pharmacological activity by inhibiting factor Xa [5]. DOACs are becoming increasingly used with respect to vitamin K antagonists due to their efficacy and

safety [6]. It appears that a reduced risk of bleeding can be observed in patients treated with DOACs compared with warfarin as a therapeutic regimen, although in some cases monitoring is still advised [7].

Patients under oral anticoagulant therapy are more prone to bleeding complications and hematoma formation following dental procedures. Tooth extractions are the most frequently performed oral surgical procedures, and bleeding or oozing are frequently occurring complications [8,9]. The surgical trauma on both hard and soft tissues can be related to the development of post-extraction bleeding, although inflammation and/or infection of the extraction site can be concurrent factors [10]. In patients treated with oral anticoagulants, the bleeding risk is enhanced; therefore, different recommendations have been proposed, including anticoagulant therapy modulation through reduction, suspension, or bridging [11]. However, it has also been suggested that therapy discontinuation may expose the patient to a higher risk of thromboembolism against a modest risk of hemorrhage in patients with an INR within the therapeutic range [12].

At present, several hemostatic agents find application for the management of post-extractive bleeding in patients treated with oral anticoagulants. The aim of the present systematic review was to analyze the hemostatic agents employed to manage the bleeding risk associated with dental extraction procedures in patients undergoing oral anticoagulant therapy with vitamin K antagonists and DOACs.

2. Materials and Methods

2.1. Study Protocol and Eligibility Criteria

The study protocol was prepared following the Preferred Reporting Items Systematic Review and Meta-Analyses Statement [13–15] and registered in PROSPERO (Prospective Register of Systematic Reviews).

The focused question of the present review was: "What are the hemostatic measures adopted in cases of bleeding following dental extractions in patients treated with oral anticoagulants?"

The following PICO (Patient, Intervention, Comparison, Outcome) was established for article inclusion:

(P) Type of participants: patients treated with oral anticoagulants
(I) Type of interventions: dental extraction, either single or multiple
(C) Comparison between interventions: any type of hemostatic measure compared with other treatments/placebo/no treatment
(O) Type of outcome measures: bleeding control following dental extraction.

The inclusion criteria were:

- Patients treated with oral anticoagulants
- Patients undergoing dental extractions
- One of the following study designs: observational studies, case-control studies, randomized controlled trials and interventional studies
- A minimum number of 10 participants in the study
- English language.

The exclusion criteria were:

- Patients not treated with oral anticoagulants
- Patients undergoing oral surgical interventions other than tooth extraction
- One of the following study designs: systematic reviews and review articles, case reports and case series
- Less than 10 participants in the study
- Articles not written in English.

No time limitations were set.

2.2. Literature Search

The electronic search was performed in PubMed and Scopus (SG) up to June 2022. The search strategy included a combination of MeSH terms and free text words:

((“Hemostatics” [Mesh] OR “Hemostatics/Pharmacological Action” [Mesh]) AND (“Tooth extraction” [Mesh] OR “Tooth Extraction/complications” [Mesh]) AND (“Anticoagulants” [Mesh] OR “Warfarin” [Mesh] OR “Phenprocoumon” [Mesh] OR “Acenocoumarol” [Mesh] OR “Factor Xa Inhibitors” [Mesh] OR “Rivaroxaban” OR “Apixaban” OR “Dabigatran”) AND (“Oral Surgical Procedures/complications” [Mesh] OR “Hemorrhage” [Mesh])).

The search was performed in dental journals. A hand search was performed to retrieve additional studies. Bibliographies of relevant papers were also checked. Trials databases such as clinicaltrial.gov were also searched.

2.3. Study Selection and Data Collection

Eligibility assessment was performed by two calibrated reviewers (RI and MN, κ-score > 0.8) for possible inclusion in the review in August 2022. Titles and abstracts were screened to retrieve the articles to be included in the full text analysis. In cases of unclear abstracts, full text analysis was performed to avoid exclusion of any potentially relevant article. The studies deemed suitable for inclusion following full text analysis underwent data extraction through an ad hoc extraction sheet.

2.4. Quality Analysis and Risk of Bias Assessment

Quality analysis was performed by three calibrated reviewers (RI, MN, SG). Risk of bias was assessed following the Cochrane Reviewers’ Handbook [16]. The following domains were classified as adequate, inadequate, or unclear:

- Random sequence generation
- Allocation concealment
- Blinding of participants, personnel, and outcome assessors
- Incomplete outcome data handling
- Selective outcome reporting.

2.5. Synthesis of the Results

Data were presented in evidence tables reporting study characteristics and main conclusions.

3. Results

3.1. Study Selection

A total of 116 articles were retrieved from literature search, 106 through electronic database searching and 10 through hand searching. Following title and abstract analysis, 91 articles were excluded. The remaining 25 articles underwent full text analysis, which further excluded three articles. A final assessment was carried out on 22 articles (Figure 1).

3.2. Study Characteristics

The study population consisted of 1276 subjects (43.8% females), with a mean age of 58.6 years (SD ± 11.9). The follow-up period varied from a minimum of one day to a maximum of 10 days. Twenty studies evaluated patients treated with Warfarin [17–36], and two studies involved patients treated with DOACs [37,38]. Nine articles evaluated the application of intra-alveolar agents [17–24]. Three articles employed tranexamic acid mouthwashes [25,26,38]. Three articles employed Platelet-Rich Fibrin (PRF) [27,28,37]. Seven articles compared different agents and administration methods [29–36]. Results are summarized in Table 1.

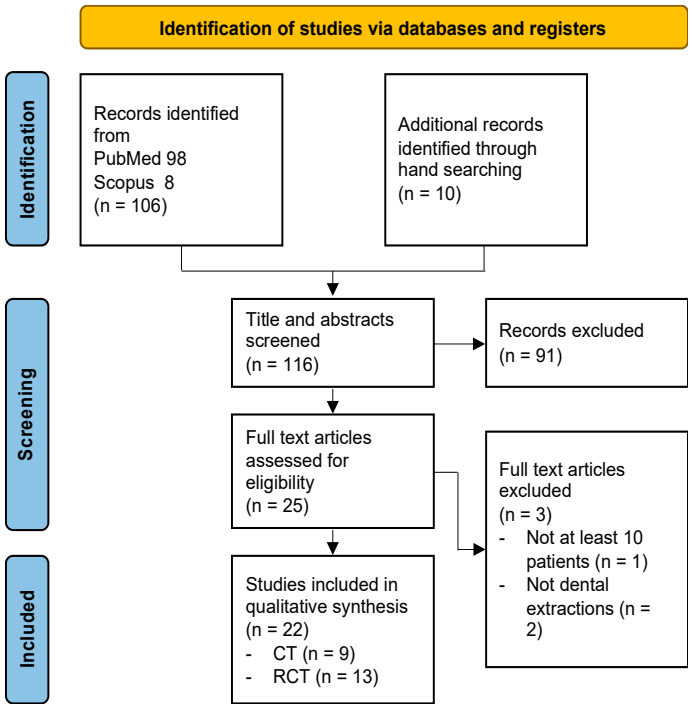

Figure 1. Literature search flowchart according to PRISMA guidelines.

3.3. Patients Treated with Warfarin

3.3.1. Intra-Alveolar Agents

Bajkin et al. [17] compared the application of gelatin sponge without suture versus suture and gauze compression in patients treated with warfarin in the therapeutic range. Of 90 patients enrolled in total, bleeding was observed in five patients and local hemostatic measures were sufficient in cases of hemorrhage. No differences between the treatment groups were noted. Çakarer et al. [18] evaluated the effectiveness of Ankaferd blood stopper (ABS) compared with gauze compression (control group). A significant difference between the groups was reported in terms of bleeding time, which was statistically lower in the ABS group ($\leq$1 min). Halfpenny et al. [19] compared two hemostatic intra-alveolar agents, oxidized regenerated cellulose (Surgicel), and fibrin adhesive (Beriplast P). No differences in post-operative bleeding were noted. The Surgicel group experienced higher levels of pain. Kumar et al. [20] compared HemCon dental dressing (HDD) with gauze compression. HDD presented significantly lower bleeding time and improved wound healing. Another study by Malmquist et al. [21] evaluated HDD effectiveness versus no treatment. In cases of treatment with HDD, hemostasis was achieved significantly sooner. HDD treated wounds achieved significantly improved healing. Okamoto et al. [22] investigated the application of (i) blue-violet LED irradiation, (ii) blue-violet LED irradiation and hemostatic gelatin sponge, and (iii) hemostatic gelatin sponge. The authors found a significantly higher percentage of hemostasis in the LED irradiation and hemostatic gelatin sponge group when compared with the hemostatic gelatin sponge group. No other significant differences were detected. Scarano et al. [23] evaluated the intra-alveolar application of calcium sulphate compared with obliterative suture. Bleeding frequency was significantly lower in the calcium sulphate group at days one and three post-op. No differences in healing were observed at five and seven days follow-up. Svensson et al. [24] employed absorbable hemostatic gelatin sponges or collagen fleece and sutures in patients with an INR $\leq$ 3.5. Of the 124 patients enrolled, five patients (4%) experienced post-op bleeding.

Table 1. Summary of main results.

Author	Setting, Funding	Study Design	Sample Size Number (% of Females), Mean Age, Number of Sites	Follow-Up	Oral Anticoagulant	Interventions	Study Conclusions
Al-Belasy et al., 2003 [29]	Dental Hospital, NR	CT	40 patients (40% F), mean age 57.2 years, non specified umber of sites	10 days	Warfarin	1. Gelatin sponge 2. N-butyl-2-cyanoacrylate glue	Histoacryl glue reduced the occurrence of spontaneous bleeding
Bajkin et al., 2014 [17]	Dental Hospital, NR	RCT	90 patients (38% F), mean age 66.1 years, 121 sites	5 days	Warfarin	1. Suture 2. Gelatin sponge 3. Gauze compression	Gauze compression controlled bleeding in patients with INR $\leq$ 3.0
Blinder et al. 1999 [30]	Dental Hospital, NR	CT	150 patients (42% F), age 35–93 years, 359 sites	7 days	Warfarin	1. Gelatin sponge and sutures 2. Gelatin sponge, sutures, and tranexamic acid mouthwash 3. Fibrin glue, gelatin sponge, and sutures	Resorbable gelatin sponge and sutures controlled bleeding following dental extractions
Çakarer et al., 2013 [18]	Dental Hospital, NR	RCT	25 patients (48% F), mean age 51.9 years, 32 sites	7 days	Warfarin	1. Gauze compression 2. Ankaferd Blood Stopper	Ankaferd Blood Stopper reduced bleeding in patients with INR $\leq$ 4.0 without interruption or reduction of the medication
Carter & Goss 2003 [25]	Dental Hospital, Public funding	RCT	85 patients (36% F), mean age 65.4 years, 152 sites	7 days	Warfarin	1. 4.8% tranexamic acid mouthwash for 2 days 2. 4.8% tranexamic acid for 5 days	Both administration protocols of 4.8% tranexamic acid mouthwash favored haemostasis in anticoagulated patients
Carter et al., 2003 [31]	Dental Hospital, NR	RCT	49 patients (36% F), mean age 65 years, 152 sites	8 days	Warfarin	1. 4.8% tranexamic acid solution 4 times a day for 7 days 2. Intra-alveolar autologous fibrin glue	Tranexamic acid mouthwash and autologous fibrin glue controlled postoperative bleeding
da Silva et al., 2018 [32]	Dental Hospital, Public funding	RCT	52 patients (53% F), mean age 61.9 years, 140 sites	7 days	Warfarin	1. Epsilon-aminocaproic acid mouthwash 2. No treatment	No differences in postoperative bleeding were observed between the study groups
de Almeida Barros Mourão et al., 2019 [37]	Dental Hospital, NR	CT	25 patients (56% F), mean age 72.44 years, 44 sites	10 days	DOACs	PRF	PRF reduced bleeding
Eldibany et al., 2014 [33]	Dental Hospital, NR	RCT	20 patients (45% F), mean age 46.5 years, non specified number of sites	10 days	Warfarin	1. PRF 2. HemCon Dental Dressing	PRF and HemCon Dental Dressing were both effective in reducing post-operative bleeding
Halfpenny et al., 2001 [19]	Dental Hospital, NR	CT	50 patients (52% F), mean age 65.6 years, non specified number of sites	7 days	Warfarin	1. Surgicel 2. Beriplast	Beriplast was as effective as Surgicel in preventing postextraction hemorrhage
Harfoush et al., 2016 [27]	Dental Hospital, NR	CT	50 patients (32% F), mean age 63 years, non specified number of sites	1 day	Warfarin	1. PRF 2. Gauze compression	Topical application of PRF reduced bleeding in patients taking warfarin

Table 1. *Cont.*

Author	Setting, Funding	Study Design	Sample Size Number (% of Females), Mean Age, Number of Sites	Follow-Up	Oral Anticoagulant	Interventions	Study Conclusions
Kumar et al., 2016 [20]	Dental Hospital, NR	RCT	30 patients (40% F), age 30–50 years, non specified number of sites	7 days	Warfarin	1. HemCon Dental Dressing 2. Gauze compression	HemCon Dental Dressing shortened bleeding time and improved wound healing
Malmquist et al., 2008 [21]	Dental Hospital, NR	RCT	17 patients (53% F), mean age 25 years, 126 sites	7 days	Warfarin	1. HemCon Dental Dressing 2. No treatment	HemCon Dental Dressing improved wound healing
Oberti et al., 2020 [34]	Private practice, NR	CT	20 patients (30% F), mean age 54.3 years, 20 sites	7 days	Warfarin	1. Calcium sulphate (CaS) 2. Gauze soaked in tranexamic acid	Calcium sulphate was effective in controlling post-operative bleeding
Ockerman et al., 2021 [38]	Dental Hospital, Public funding	RCT	218 patients (33% F), mean age 73.75 years, 272 sites	7 days	DOACs	1. 10% tranexamic acid mouthwash 2. Placebo mouthwash	10% tranexamic acid mouthwash did not reduce bleeding after dental extraction
Okamoto et al., 2014 [22]	Dental Hospital, NR	RCT	48 patients (41% F), mean age 67.79 years, non specified number of sites	1 day	Warfarin	1. Irradiatetion with blue-violet LED 2. Hemostatic gelatin sponge and LED irradiation 3. Hemostatic gelatin sponges	Hemostatic gelatin sponge and LED irradiation reduced postoperative bleeding
Pippi et al., 2015 [35]	Dental Hospital, NR	CT	25 patients (20% F), mean age 70.45 years, 50 sites	5 days	Warfarin	1. HemCon Dental Dressing 2. Collagen hemostatic sponge	HemCon Dental Dressing improved tissue healing
Queiroz et al., 2018 [26]	Dental Hospital, Public funding	RCT	37 patients (62% F), mean age 45.5 years, 37 sites	7 days	Warfarin	1. Saline 2. Tranexamic acid	Tranexamic acid controlled intermediate hemorrhage in the first 24 h post-op
Sammartino et al., 2011 [28]	Dental Hospital, NR	CT	50 patients (56% F), age 47–67 years, 168 sites	7 days	Warfarin	PRF	PRF reduced post-operative bleeding
Scarano et al., 2014 [23]	Dental Hospital, NR	RCT	30 patients (73% F), mean age 54.6 years, 42 sites	7 days	Warfarin	1. Obliterative suture 2. Intra-alveolar calcium sulfate	Calcium sulfate controlled bleeding following dental extraction
Soares et al., 2015 [36]	Dental Hospital, NR	RCT	41 patients (33% F), mean age 51.1 years, 93 sites	7 days	Warfarin	1. Tranexamic acid 2. Gelatin sponge 3. Gauze compression	Compression with dry gauze without hemostatic agents was an effective hemostatic measure
Svensson et al., 2013 [24]	Dental Hospital, NR	CT	124 patients (44% F), mean age 71 years, 194 sites	10 days	Warfarin	Hemostatic gelatin sponge/collagen fleece and sutures	Local hemostatics and sutures effectively controlled post-operative bleeding

3.3.2. Tranexamic Acid Mouthwashes

Carter & Goss [25] compared two administration protocols of 4.8% tranexamic acid mouthwash, which was prescribed for either two or five days post-op. No statistically significant difference was observed between groups in post-op bleeding depending on the duration of tranexamic acid mouthwash treatment. Queiroz et al. [26] performed alveolar irrigation following dental extraction with either 250 mg/5 mL tranexamic acid or saline. In the tranexamic acid group, hemostasis was obtained in a significantly shorter time compared with the saline group.

3.3.3. Platelet-Rich Fibrin

Harfoush et al. [27] compared the application of PRF in the post-extractive socket versus no treatment (control group). Patients treated with PRF experienced mild (20%) or moderate (80%) bleeding, while patients in the control group showed moderate (28%) or severe (72%) bleeding. Sammartino et al. [28] employed Leukocyte- and Platelet-Rich Fibrin (L-PRF). The authors encountered hemorrhagic complications in 4% of cases, while 20% of patients showed mild post-op bleeding. The bleeding episodes were limited to the first two h post-op, in the lack of delayed bleeding episodes.

3.3.4. Comparison Studies

Al-Belasy et al. [29] compared the hemostatic effects of n-butyl-2-cyanoacrylate glue and gelatin sponge (control group). The occurrence of post-op spontaneous bleeding requiring treatment was significantly higher in the control group. No differences in wound healing were detected at 10 days follow-up. Blinder et al. [30] compared three different protocols, specifically (i) gelatin sponge and sutures, (ii) gelatin sponge, sutures, and tranexamic acid mouthwash, and (iii) fibrin glue, gelatin sponge, and sutures. Post-operative bleeding was observed in 8.6% of cases. The authors concluded that local hemostasis with resorbable gelatin sponge and sutures was sufficient in managing the bleeding risk in patients treated with oral anticoagulants. Carter et al. [31] compared the prescription of 10 mL rinse with a 4.8% tranexamic acid solution four times a day for seven days postoperatively versus intraoperative application of autologous fibrin glue. No statistically significant difference was found between the groups in terms of post-op bleeding. da Silva et al. [32] assessed the effectiveness of epsilon-aminocaproic acid administration, either as an intra-alveolar agent or as a mouthwash to be employed in the post-op period. No statistically significant difference in late bleeding was observed between the groups. Eldibany et al. [33] compared the application of intra-alveolar PRF and HDD. No statistically significant difference was found between the groups in terms of post-op bleeding. The PRF group experienced minimal pain and accelerated healing, while the HDD group presented moderate/severe pain in the first few days post-op and retarded healing. In the HDD group, the occurrence of some cases of alveolar osteitis was registered. Oberti et al. [34] evaluated the intra-alveolar application of calcium sulphate versus compression with a gauze soaked in tranexamic acid (control group). Post-operative bleeding at one-day post-op was significantly higher in the control group. At seven days post-op, there were no differences between the two groups. Pippi et al. [35] employed either HDD or hemostatic sponge as intra-alveolar agents. No statistically significant differences in bleeding time were observed between the groups. Postoperative pain was significantly lower in the HDD group than in the hemostatic sponge group. Improved healing was obtained in the HDD group in 85% of cases. Soares et al. [36] compared eight min compression with a gauze soaked in 4.8% tranexamic acid, intra-alveolar application of a fibrin sponge, and eight min compression with a dry gauze. No difference in bleeding events was observed among the groups.

3.4. Patients Treated with DOACs

3.4.1. Tranexamic Acid

Ockerman et al. [38] performed a placebo-controlled trial on the use of 10% tranexamic acid mouthwash 3-times-a-day for 3 days in patients treated with DOACs (Rivaroxaban, Apixaban, Edoxaban, Dabigatran). No differences were found between the groups in terms of post-extraction bleeding, number of bleeding events, and procedural bleeding score. Delayed bleeding and bleeding after multiple extractions showed lower occurrence in the tranexamic acid group.

3.4.2. PRF

de Almeida Barros Mourão et al. [37] employed PRF as hemostatic agents in patients treated with Rivaroxaban or Apixaban. In all cases post-op bleeding was successfully arrested by PRF in all patients. No bleeding complications were observed at 24 and 48 h post-op. No alveolar infection was detected at 7-days post-op, and favorable wound healing was observed in all patients at 10 days follow-up.

3.5. Risk of Bias in Interventional Studies

Results of risk of bias analysis are reported in Table 2. Four studies [26,35,36,38] were judged at moderate risk of bias. Eighteen studies were assigned a high risk of bias [17–25,27–34,37]. None of the studies included was deemed at low risk of bias for all domains.

Table 2. Quality analysis of the included studies. Color coding: WHITE: not applicable; YELLOW: unclear; GREEN: adequate; RED: inadequate.

Authors	Study Design	Setting	Funding	Randomization	Allocation Conealment	Operators Blinding	Missing Outcome Data Reported	Missing Outcomes Were Balanced among Groups	Reasons for Dropout Clearly Specified	Selective Outcome Reporting	Therapist Experience	Statistical Method	Sample Size Estimation	Examiner Calibration
Al-Belasy et al., 2003 [29]	CT	Dental Hospital	NR	NA	NA	NA	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate	Inadequate	Inadequate
Bajkin et al., 2014 [17]	RCT	Dental Hospital	NR	Unclear	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate	Inadequate	Inadequate
Blinder et al. 1999 [30]	CT	Dental Hospital	NR	NA	NA	NA	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate	Inadequate	Inadequate
Çakarer et al., 2013 [18]	RCT	Dental Hospital	NR	Inadequate	Inadequate	Inadequate	Unclear	Unclear	Unclear	Adequate	Unclear	Unclear	Inadequate	Inadequate
Carter & Goss 2003 [25]	RCT	Dental Hospital	Public funding	Adequate	Adequate	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear	Unclear	Inadequate	Inadequate
Carter et al., 2003 [31]	RCT	Dental Hospital	NR	Inadequate	Inadequate	Inadequate	Inadequate	Unclear	Unclear	Adequate	Unclear	Inadequate	Inadequate	Inadequate
da Silva et al., 2018 [32]	RCT	Dental Hospital	Public funding	Adequate	Adequate	Adequate	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Inadequate	Inadequate
de Almeida Barros Mourão et al., 2019 [37]	CT	Dental Hospital	NR	NA	NA	NA	Unclear	Unclear	Unclear	Adequate	Adequate	Inadequate	Inadequate	Inadequate
Eldibany et al., 2014 [33]	RCT	Dental Hospital	NR	Inadequate	Inadequate	Inadequate	Inadequate	Unclear	Unclear	Adequate	Unclear	Inadequate	Inadequate	Inadequate
Halfpenny et al., 2001 [19]	CT	Dental Hospital	NR	NA	NA	NA	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate	Inadequate	Inadequate
Harfoush et al., 2016 [27]	CT	Dental Hospital	NR	NA	NA	NA	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Inadequate	Inadequate
Kumar et al., 2016 [20]	RCT	Dental Hospital	NR	Adequate	Adequate	Adequate	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Adequate	Inadequate
Malmquist et al., 2008 [21]	RCT	Dental Hospital	Industry	Inadequate	Inadequate	Inadequate	Unclear	Unclear	Unclear	Adequate	Unclear	Unclear	Inadequate	Inadequate
Oberti et al., 2020 [34]	CT	Private practice	NR	NA	NA	NA	Unclear	Unclear	Unclear	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate

Table 2. *Cont.*

Authors	Study Design	Setting	Funding	Randomization	Allocation Conealment	Operators Blinding	Missing Outcome Data Reported	Missing Outcomes Were Balanced among Groups	Reasons for Dropout Clearly Specified	Selective Outcome Reporting	Therapist Experience	Statistical Method	Sample Size Estimation	Examiner Calibration
Ockerman et al., 2021 [38]	RCT	Dental Hospital	Public funding	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate	Adequate	Unclear
Okamoto et al., 2014 [22]	RCT	Dental Hospital	NR	Inadequate	Inadequate	Inadequate	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Inadequate	Inadequate
Pippi et al., 2015 [35]	CT	Dental Hospital	NR	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Adequate	Unclear
Queiroz et al., 2018 [26]	RCT	Dental Hospital	NR	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Unclear
Sammartino et al., 2011 [28]	CT	Dental Hospital	NR	NA	NA	NA	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Inadequate	Inadequate
Scarano et al., 2014 [23]	RCT	Dental Hospital	NR	Inadequate	Inadequate	Adequate	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Inadequate	Inadequate
Soares et al., 2015 [36]	RCT	Dental Hospital	NR	Unclear	Unclear	Adequate	Unclear	Unclear	Unclear	Adequate	Unclear	Adequate	Adequate	Unclear
Svensson et al., 2013 [24]	CT	Dental Hospital	NR	NA	NA	NA	Unclear	Unclear	Unclear	Adequate	Unclear	Inadequate	Inadequate	Inadequate

4. Discussion

The issue of post-operative bleeding is gaining importance due to the high number of patients treated with oral anticoagulants. Although DOACs are becoming widely prescribed, there is still limited evidence on the hemostatic measures which could be applied in these patients. Conversely, the management of patients treated with warfarin has been extensively explored, with the adoption of various protocols for the limitation of bleeding risks.

Intra-alveolar agents appear the most effective measure for post-op bleeding prevention. In all of the studies reporting on intra-alveolar agents [17–24,29,30,32,34,35], adequate hemostasis was observed, although in most cases in the absence of a statistically significant difference with control groups. This finding agrees with the recent systematic review by Moreno Drada et al. [39], as the authors concluded that no superiority could be determined for one hemostatic agent over the others. In particular, the authors highlighted that due to a high risk of bias, the certainty of the evidence was low. Moreover, no differences in terms of bleeding events and bleeding time were detected when comparing different hemostatic interventions [39]. Importantly, it should be noted that the present evidence was exclusively based on patients treated with warfarin.

The application of tranexamic acid was reported in six studies, with different administration protocols [25,26,31,34,36,38]. In all of the described cases, the application of tranexamic acid reduced the bleeding time. However, most of the studies were performed on patients treated with warfarin, and only one study [38] was performed in patients treated with DOACs. As reported in the systematic review by Engelen et al. [40], local application of tranexamic acid may prevent oral bleeding in patients treated with warfarin undergoing minor oral surgery or dental extractions. In fact, the authors found that tranexamic acid mouthwash reduced the bleeding rate following dental extractions by 25% if compared with the placebo, but there were no significant differences when compared with gauze compression or suture [40]. Consistent with previous literature, our study highlights a lack of evidence in patients treated with DOACs. Therefore, definitive conclusions could not be drawn either on the actual efficacy of antifibrinolytic therapy or the beneficial effects on patients treated with DOACs.

PRF application was reported in two studies conducted on patients taking warfarin 24, 25 and in one study on patients treated with DOACs [37]. In all of the studies, the available evidence supported the application of PRF in limiting the bleeding complications in the early post-op period, in the absence of episodes of delayed bleeding. This finding appears in contrast with the evidence from a recent systematic review by Filho et al. [41], where the authors concluded that hemorrhagic complications after dental extractions cannot be prevented with the application of PRF in patients on oral anticoagulant therapy. Moreover, no effects on pain reduction or on postoperative alveolitis development were detected in anticoagulated individuals [41].

The present study has some limitations. First, the paucity of studies evaluating patients treated with DOACs hindered the drawing of firm conclusions on this increasingly employed class of anticoagulants. Secondly, the heterogeneity in the methodologies reported in the included studies did not allow the performance of meta-analyses. Similarly, the presence of different comparative groups could also be a confounding factor. Finally, the included studies were all at moderate/high risk of bias, thus affecting reliability of the analysis.

Although the superiority of one hemostatic measure above the other cannot to date be stated in patients taking oral anticoagulants, it should be noted that such measures require further investigation even in the presence of other systemic conditions affecting coagulation capacity. Considering medication induced bleeding risk, some studies addressed the issue of antiplatelet therapy in the dental setting. Although this topic falls beyond the scope of the present review, it is important to mention how antiplatelet drugs, used alone (single antiplatelet therapy, SAPT), or in combination (dual antiplatelet therapy, DAPT) may affect clotting formation, leading to prolonged post-extraction bleeding and hemorrhagic

complications [42]. Current literature reports that the use of local hemostatic agents may be sufficient in managing the bleeding risk without changing the algorithm of antiplatelet therapy [43]. From this perspective, the performance of randomized clinical trials to further assess the role of hemostatic agents following dental surgery is advised, taking into account a broader variety of systemic conditions.

5. Conclusions

The current evidence on the effectiveness of hemostatic measures appears to be still limited. Indeed, the presence of studies at moderate/high risk of bias and the paucity of studies regarding hemostasis in patients treated with DOACs hinder the possibility of drawing firm conclusions. Further research is advised to increase the level of evidence of the application of hemostatic agents in patients treated with oral anticoagulants.

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