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HIP FRACTURES IN ADULTS

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REVIEW ARTICLE

Thromboprophylaxis and Blood Transfusion in Hip Fractures

Abstract

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Advancement in medical technology has increased the life expectancy of people, leading to a significant rise in geriatric fractures. Hip fracture in particular is in rise with associated high morbidity and mortality. Venous thromboembolism and perioperative anemia due to blood loss or chronic conditions are major complications influencing patient outcomes. Though thromboprophylaxis and blood transfusion practices have evolved significantly, there still persist debates regarding the most effective management strategies. In major part across the world, Low-molecular-weight heparin remains the standard for venous thromboembolism prophylaxis, however direct oral anticoagulants are increasingly being investigated and used in orthopedic trauma. Restrictive transfusion strategies have shown safety and potential benefits in reducing complications. However, individual patient factors play major role in their subsequent management. Thromboprophylaxis and transfusion strategies in hip fracture surgery should be individualized as per the patient and institutional protocol for optimization. Emerging data support broader use of DOAC as per the protocol practice. The restrictive targeted transfusion remains safe in most patients. Future research should clarify optimal protocol in high-risk population. This article aims to discuss current evidence and guidelines regarding thromboprophylaxis and blood transfusion in hip fracture surgery and highlight recent advances and ongoing challenges.

KEYWORDS
Blood transfusion, Hip fracture, Thromboprophylaxis, Venous thromboembolism

Introduction

With increase in life expectancy, there is exponential rise in the number of hip fractures. This represents a global health problem in the elderly population. Geriatric hip fractures have high rates of morbidity and mortality with subsequent socioeconomic burden.[1–4] Literature reports, over 1.6 million hip fractures occur in a year with the number projected to surpass 6 million by 2050.[3,4] Management of thromboprophylaxis and anemia correction is crucial for optimizing patient outcomes perioperatively.[5,6] Historically, the incidence of asymptomatic deep vein thrombosis (DVT) without prophylaxis ranged between 40% to 80%, while the incidence of symptomatic venous thromboembolism (VTE) ranged between 0.5% to 1.5%.[7,8] In a prospective observational study of 66 patients over the age of 44 years who underwent surgical treatment for hip fracture in Tribhuvan University Teaching Hospital in Nepal, the incidence of DVT was 8%.[9]

With the belief that higher hemoglobin level would improve outcomes, blood transfusion practices were once liberal. However, due to transfusions risks, including transfusion related acute lung injury, circulatory overload, immunomodulation, infection, increased length of hospital stays, and mortality, blood transfusion practices have become restrictive.[10–12] Management of hip fracture in elderly patients has advanced significantly. In the western world, direct oral anticoagulants (DOAC) are emerging as a potential alternative to low molecular weight heparin (LMWH) for thromboprophylaxis, while restrictive transfusion strategies and development of patient blood management (PBM) protocols have largely replaced liberal transfusion policies.[13–15] This review synthesizes developments in thromboprophylaxis and blood transfusion strategies in hip fracture patients, drawing on the latest evidence from 2010 to 2024.

Thromboprophylaxis in Hip Fractures

Risk of Venous Thromboembolism (VTE)

Major orthopedic fractures itself is an independent risk factor for DVT. It may be further aggravated by immobility, associated comorbidities and surgery induced hypercoagulability.[7,16]According to Scottish guidelines network (SIGN) (https://www.sign.ac.uk/media/1060/sign122.pdf), major risk factors for DVT includes age, obesity, varicose vein, family history of VTE, thrombophilia, combined oral contraceptives, hormone replacement therapy, pregnancy, immobility, puerperium, hospitalization, anesthesia and indwelling central venous catheter. It has been shown that asymptomatic DVT rise to 40-80% without prophylaxis.[7,8] Pulmonary embolism (PE) remains a significant contributor to perioperative mortality, underlining the critical role of thromboprophylaxis strategies.[17] (Table 1)

Table 1. Risk factors for thromboembolism[18]

Intrinsic factors	Increasing Age
	Previous history of thromboembolism
	Family history in first-degree relatives
	Thrombophilia (e.g., Factor V Leiden)
Associated Comorbidities	Obesity (BMI ≥30 kg/m2)
	Immobility
	Smoking
	Active malignancy
	Cardiac disease
	Medication (e.g., hormonal therapy/oral contraceptive)
Specific fractures	Spinal fractures
	Pelvis/ Acetabular fractures
	Hip fractures

BMI Body Mass Index

Pharmacological Options

Lower Molecular Weight Heparin (LMWH)

LMWH has long been established as the gold standard for thromboprophylaxis for any traumatic incident including the hip fracture. LMWH as compared to Unfractionated Heparin (UFH) offers several advantages. Studies in past two decades shows superiority of LMWH with lower rates of both symptomatic and asymptomatic VTE, acceptable bleeding profile, predictable pharmacokinetics, ease of administration without the need for routine monitoring, longer half-life and a lower incidence of heparin induced thrombocytopenia (HIT).[19] Consequently, major guidelines-including those from the American College of Chest Physicians (ACCP)-recommend LMWH as the first-line therapy unless contraindicated.[20] Mismetti et al. (2004) also found LMWH as superior to Vitamin K antagonists (VKA) and at least equivalent to Fondaparinux in efficacy, with better tolerability and fewer monitoring demands.[21]

Emergence of Direct Oral Anticoagulants (DOAC)

The past decade has witnessed growing interest in DOAC for thromboprophylaxis of hip fracture that includes Rivaroxaban, Apixaban, Edoxaban, Betrixaban and Dabigatran. Trial such as RE-NOVATE demonstrated the non-inferiority of Dabigatran compared to Enoxaparin for VTE prevention in elective hip arthroplasty.[22]A 2023 meta-analysis found DOAC were not inferior to LMWH regarding VTE prevention and risk of bleeding in hip fracture surgery, though results were underpowered and limited to small Asian cohorts. Thus, while promising, DOAC should be used cautiously until further large-scale studies confirm their safety and efficacy in general population.[23,24] Nevertheless, cost considerations limit DOAC use.[25] (Table 2)

Critical Appraisal of DOAC Evidence

Pharmacological options for VTE prophylaxis are the cornerstone of perioperative care in orthopedic surgery. Among newer agents,

Table 2. Pharmacokinetics and pharmacodynamics of Direct Oral Anticoagulants[26]

DOAC	Dabigatran	Rivaroxaban	Apixaban	Endoxaban	Betrixaban
Target	Thrombin (Factor IIa)	Factor Xa	Factor Xa	Factor Xa	Faxtor Xa
Drug half-life T½ (hours)	12-17	Young: 5-9; Elderly: 11-13	8-15	10-14	19-27
T_{max} (hours)*	2	2-4	1-3	1-2	3-4
Bioavailability (%)	7	66	50	62	34
Renal excretion (%)	80	66	25	35	17.8
Fecal excretion (%)	82-88	26.4	46.7-56	62.2	85
CYP450 metabolism	No	Yes	Yes	No	No
Reversal agents	Idarucizumab	Andexanet alfa	Andexanet alfa	-	-
Time allotted prior to spinal anaesthesia (hours)	24	24	24	24	72

*Time to reach peak concentration in plasma after oral dose; *CYP* Cytochrome P450

DOAC have brought convenience and potentially improved patient adherence, yet their role in hip fracture surgery remains controversial. Several clinical trials and reviews demonstrate that DOAC are effective alternatives to LMWH in elective joint replacement, but their safety and efficacy in trauma patients remain understudied.[27–29] Hip fracture patients are generally older, frailer, and have higher bleeding risks than the populations included in pivotal DOAC trials.

In a 2021 meta-analysis, You et al. found no significant mortality benefit in delaying surgery to allow DOAC clearance.[30] Moreover, studies have reported increased morbidity rates in a patient delayed for surgery due to ongoing use of DOAC.[30] However, these complications may stem more from institutional protocols (e.g., unnecessary preoperative delays) than effects of intrinsic drug. The limited available data to support optimal resumption timing post-operatively and inadequate evidence of extended prophylaxis duration (> 14 days) are some drawbacks of using DOAC. Thus, they should be used cautiously and selectively, ideally in patients with preserved renal function and low bleeding risk. Larger, well-designed randomized controlled trial specific to hip fracture patients are needed to provide evidence for using DOAC.

Duration of Thromboprophylaxis

Evidence supports extended pharmacologic prophylaxis for 28-35 days following hip fracture surgery, especially in high-risk individuals. This is based on persistent hypercoagulability and reduced venous function lasting several weeks post-injury. ACCP and SIGN (https://www.sign.ac.uk/media/1060/sign122.pdf) recommend a minimum duration of 10-14 days, with consideration for prolongation based on patient mobility status, comorbidities, and bleeding risk.[28]

Mechanical Thromboprophylaxis

Mechanical methods of thromboprophylaxis includes early mobilization, intermittent pneumatic compression devices (IPCD), anti-embolism stockings and venous foot pumps. IPCD remain a valuable adjunct particularly for patients with high risk of bleeding. IPCD doesn't increase the risk of bleeding because it doesn't alter the clotting cascade. The disadvantages of mechanical prophylaxis are poor compliance; cost of the devices and low efficacy compared to pharmacological methods. Many studies consistently show that pharmacologic agents are superior to mechanical methods of thromboprophylaxis.[28–31]

Aspirin

Acetylsalicyclic acid (Aspirin) is an oral drug that inhibits the activity of cyclooxygenase in platelets. It is an effective, inexpensive and safe form of VTE prophylaxis in total joint arthroplasty. However, its role as a drug for VTE prophylaxis in hip fracture is controversial. Major Extremity Trauma Research Consortium (METRC) published in 2023 concluded that thromboprophylaxis with aspirin was noninferior to LMWH in preventing death and was associated with low incidence of DVT and pulmonary embolism (PE) and low 90-day mortality.[32]

Williamson TK et al. (2024) did a systematic review and meta-analysis to assess the effectiveness of Aspirin to other agents in preventing VTE

and mortality following hip fracture surgery.[33] They concluded that Aspirin demonstrated similar protective effects on prevention of VTE compared to other agents and may have significant protective effects on overall mortality following surgical intervention for hip fractures. However, the current evidence concerning its use in hip fracture patients is less than robust, with more than half of the studied outcomes considered statistically fragile.

International Thromboprophylaxis Guidelines for hip fracture surgery

Based on a review on thromboembolism prophylaxis, Felvas DA et al. (2018) recommends the ACCP guidelines for daily clinical practice.[34] The ACCP guidelines recommend the use of LMWH, low-dose UFH, adjusted-dose vitamin K antigonists (VKA), Fondaparinux, Aspirin or and IPCD for at least 10-14 days and up to 35 days.[28] The use of LMWH is recommended in preference to other chemical agents. In hip fracture surgery, LMWH is recommended to be administered either 12 hours or more pre-operatively or 12 hours or more post-operatively. During hospitalization, use of dual prophylaxis with and IPCD device for at least 18 hours daily along with an antithrombotic agent is recommended. Doppler USG screening before hospital discharge is not recommended for asymptomatic patients.[18]

SIGN guidelines (https://www.sign.ac.uk/media/1060/sign122.pdf) recommend using LMWH, UFH or Fondaparinux in combination with mechanical prophylaxis in hip fracture surgery but does not recommend Aspirin monotherapy as an appropriate pharmacological VTE prophylaxis in hip fracture surgery. According to this guideline, in patients without contraindication, Fondaparinux should be started 6 hours or more after surgery. The recommended duration of thromboprophylaxis is 4 weeks.

Recent review by Ktistakis et al. (2016) suggested that LMWH should be started on admission of the patient with a hip fracture, stopped 12 hours before surgery and restarted 6 to 12 hours postoperatively.[35]

Sen et al. (2011) in a systematic review of thromboprophylaxis in Indian patients sustaining major orthopaedic trauma recommended routine chemoprophylaxis using LMWH after hemodynamic stabilization.[36] Patients with head injury, incomplete spinal cord injury or any other contraindication for chemoprophylaxis is advised for mechanical prophylaxis. (Table 3)

Table 3. International Guidelines on Thromboprophylaxis in Hip Fractures

Guideline	Year	Recommended Agents	Duration	Comments
ACCP (Chest)	2012	LMWH preferred; alternatives: Fondaparinux, DOAC, Aspirin (select patients)	Minimum 10–14 days, extend up to 35 days	Mechanical prophylaxis if pharmacologic agents contraindicated
SIGN	2014	LMWH or Fondaparinux preferred; consider DOAC	4 weeks	High-risk patients need longer duration of prophylaxis Simultaneous use of mechanical prophylaxis
AAOS CPG[37]	2016	LMWH, Fondaparinux, DOAC, Aspirin acceptable	Minimum 10–14 days	Individual risk assessment strongly advised
NICE (NG89)	2018	LMWH first-line; Fondaparinux as alternative; Aspirin only in arthroplasty	1 month	Emphasis on early mobilization

ACCP American College of Chest Physicians; *SIGN* Scottish Intercollegiate Guidelines Network; *AAOS* American Academy of Orthopaedic Surgeons; CPG Clinical Practice Guidelines ; *NICE* National Institute for Health and Care Excellence

Blood transfusion Strategies in Hip Fracture

Historical Perspective

In the western world, blood transfusion in hip fractures surgery followed liberal threshold with the belief of early recovery with maintenance of hemoglobin (Hb) above 10 gm/dL.[12] However, blood transfusion is not without risk as transfusion related acute lung injury (TRALI), transfusion related immunomodulation (TRIM), risk of infection, volume overload and increased risk of mortality can occur.[38] Blood transfusion is indicated in trauma patients with acute hemorrhage of ≥25% total blood volume. In a normovolemic patient without cardiac disease, adequate oxygenation can be maintained with a hemoglobin level of 7 gm/dL; however, comorbidities may necessitate transfusion at a higher threshold.[39] The decision to transfuse blood should be guided by the clinical situation and not by an arbitrary laboratory value. On average, transfusion of one unit of packed

Table 4. International Guidelines on Blood Transfusion in Hip Fractures

Guideline	Year	Transfusion Threshold	Comments
WHO PBM Guidelines[42]	2021	Encourage restrictive transfusion and PBM practices	Emphasis on PBM strategies like IV iron, minimizing transfusions whenever possible
FOCUS Trial	2011	Compared Hb ≤10 gm/dL vs ≤8 gm/dL	No significant difference in mortality or functional outcomes; supports restrictive approach
NICE	2015	Restrictive strategy recommended; generally, Hb ≤ 7–8 gm/dL	Emphasizes clinical judgement and symptoms over absolute thresholds
AAOS CPG	2016	Hb ≤ 8 gm/dL for asymptomatic patients	Higher threshold (e.g. 9-10 gm/dL) may be considered in symptomatic or cardiac patients
AABB	2023	Hb ≤ 8 gm/dL for stable patients undergoing orthopaedic surgery	Individualize in cardiac disease; symptoms dictate transfusion decisions

WHO World Health Organization; *PBM* Patient Blood Management; *IV* Intravenous; *FOCUS Trial* Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair Trial; *Hb* Hemoglobin; *NICE* National Institute for Health and Care Excellence; *AAOS CPG* American Academy of Orthopaedic Surgeons Clinical Practice Guideline; *AABB* Association for the Advancement of Blood & Biotherapies

red blood cells (PRBC), results in a hemoglobin increment of one gm/dL in an adult with stable blood volume.[40]

Restrictive Vs Liberal Blood Transfusion Strategies

In 2011, Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial was conducted comparing the liberal (Hb<10 gm/dL) vs restrictive (Hb<8 gm/dL) transfusion strategy in elderly hip fractures.[12] It concluded that postoperative hemoglobin threshold of 8 gm/dL in the absence of symptomatic anemia appears to be acceptable in elderly patients with or at risk of ischaemic heart disease.[12] This showed that there was no significant differences in mortality, myocardial infarction or functional recovery in between these two groups supporting the restrictive transfusion threshold. Meta-analysis by Carson et al. (2016) also confirmed that restrictive transfusion threshold (Hb< 7-8 gm/dL) are safe in surgical patients.[10]

However, in certain scenario as in cardiovascular disease patient may benefit from maintaining higher hemoglobin level to avoid myocardial ischemia.[14] In 2023, AABB (formerly the American Association of Blood Bank) guidelines recommend individualizing transfusion decisions in patients based on overall clinical context and considering alternative therapies to transfusion.[41] It recommends using restrictive threshold of 8 gm/dL in patients with preexisting cardiovascular disease and those undergoing cardiac or orthopedic surgery. (Table 4)

Real World Data

Despite evidence supporting restrictive threshold for blood transfusion, real world implementation remains inconsistent. In Denmark, national guidelines introduced in 2018 reduced transfusion rates and mortality.[11] Conversely, Scotland's national audit in 2024 reported a transfusion rate of 28.7% after hip fracture surgery, with transfusion linked to higher 30- and 60-days mortality.[43] However, these association may reflect greater frailty of the transfused patients rather than the causation.

Patient Blood Management (PBM)

Intravenous Iron

An emerging element of PBM is the use of intravenous (IV) iron to reduce perioperative anemia and transfusion rates. In 2022, meta-analysis of eight studies showed decrease in transfusion rate with the use of iron with or without Erythropoietin.[44] IV iron in spite of its promising nature needs further research to clarify on its impact on the long-term recovery.

Tranexamic Acid (TXA)

This antifibrinolytic agent has become widely accepted in hip fracture surgery to reduce blood loss. Large meta-analysis confirms the efficacy of TXA without significant increase in thromboembolic events.[45] Poeran et al. (2014) reported reduced transfusion rates and complications in hip fracture surgery among patients receiving TXA.[46] As a result, many guidelines recommend TXA as the standard practice. Bashar et al. (2019) did a systematic review and meta-analysis of Tranexamic acid (TXA) in hip fracture surgery.[47] They concluded that there was a significant reduction in transfusion requirements when TXA was used. However, because of small sample size and low event rates for adverse effects, definitive conclusion

could not be made about its adverse effects. In 2022, Panagoitis et al. did a meta-analysis of randomized controlled trials to assess the efficacy and safety of intravenous TXA administration in elderly patients undergoing hip fracture surgery focusing on the effect of various dosages.[48] They concluded that a single pre-operative intravenous dose of 15 mg/kg TXA can safely and effectively reduce perioperative blood loss and transfusion rates in hip fracture surgery. A second post-operative dose of TXA is not associated with any statistically significant benefit. No increase in thromboembolic events' rate was observed after TXA use in geriatric population.

Machine Learning Approaches

The future of PBM may lie in predictive analytics. In 2024, Guo et al. developed a XGBoost machine learning model to predict transfusion needs in hip fracture surgery with high accuracy.[49] Such tools could individualize transfusion decisions and optimize resource allocation but practical implementation remains in the early stages and further validation is required.

Integrated Thromboprophylaxis & PBM

Modern hip fracture care demands an integrated strategy balancing thromboprophylaxis and blood management. Evidence from recent years suggests, LMWH remains the first line of thromboprophylaxis, with DOAC as a viable alternative in selected patients. Extended thromboprophylaxis of 30-35 days reduces late VTE risk, but patient selection is crucial.[17,20,24] Restrictive strategies of blood transfusion (Hb≤ 7-8 gm/dL) are safe for most patients, but higher threshold may be appropriate in patients with cardiac diseases.[12,15] PBM strategies with IV iron and TXA effectively reduce transfusion needs, while emerging machine learning tools may guide personalized perioperative care.[45,46,49]

Future Directions

In spite of the significant advancement in thromboprophylaxis and transfusion protocols, further research is required to clarify the role of DOAC in hip fracture in elderly population, especially in patients with renal impairment and high bleeding risk. More study has to be done for estimation of optimal transfusion threshold in patients with significant cardiovascular disease. High quality study is required to validate predictive models for transfusion and VTE risk to implement in general population.

Conclusion

Driven by the high-quality evidence and real-world experience in past decade, there has been significant improvement in perioperative management of hip fracture. Low molecular weight heparin (LMWH) remains the cornerstone of thromboprophylaxis worldwide, though use of direct oral anticoagulants (DOAC) is on the rise that offer effective alternative with potential advantages but high cost.

Supported by robust trials and guidelines with caution in cardiovascular disease, restrictive transfusion strategy has become the standard protocol. Patient blood management strategies to reduce the transfusion rate include giving intravenous iron, Erythropoietin and Tranexamic acid. Emergence of machine learning intelligence holds promise but require further validation. Future research should focus on refining patient selection, integrating novel therapies, and standardizing best practices to optimize the outcome in patients with hip fracture.

Conflict of Interest

None

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