Interruption of long-term warfarin is not necessary in patients undergoing total hip arthroplasty

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ABSTRACT

Introduction: The management of anticoagulation in patients undergoing arthroplasty remains a challenge. Guidelines for perioperative management of long-term warfarin recommend discontinuation of warfarin preoperatively in low risk patients. We hypothesised that patients who had their warfarin continued during the perioperative period would have shorter hospital stay and no significant increase risk of surgical complications compared to patients who had their warfarin interrupted.

Methods: This was a retrospective review of 20 consecutive patients receiving long-term warfarin who underwent total hip replacement without stopping warfarin. As a control group, we collected same data from 20 age and gender matched patients also on long term warfarin but their warfarin was stopped prior to surgery and restarted postoperatively.

Results: There was no significant difference in age, BMI or comorbidities between the 2 groups. There was a statistically significant difference between the two groups in postoperative INR ($P < 0.0001$) levels. The mean drop in Hb postoperatively was 25.95 g/L in the warfarin group and 35.7 g/L in the control group, which was statistically significant ($P = 0.0066$). Hospital stay was statistically significant with shorter stay observed in the warfarin group ($P = 0.0447$). The odds ratio for developing a postoperative complication was 1.5882 which was not statistically significant ($P = 0.6346$).

Conclusion: Our results support the hypothesis that it is safe to continue warfarin in patients on long term anticoagulation undergoing total hip replacement. Continuation of warfarin was associated with significantly shorter hospital stay and less INR fluctuations. There was no significant increase in the risk of complications or blood transfusion.

1. Introduction

Total hip replacement (THR) is one of the most successful orthopaedic operations with a total of 101,651 operations performed in the UK in 2016.¹ As the prevalence of osteoarthritis (OA) increases with age, the coexistence of significant patient comorbidities become more common.² There has been an associated increase in the number of patients undergoing hip arthroplasty surgery who are on chronic oral anticoagulants. The most common indications for oral anticoagulation are atrial fibrillation, mechanical heart valves and venous thromboembolism.³

The management of anticoagulation in patients undergoing surgical procedures remains a challenge. Consensus guidelines for the perioperative management of these patients recommend discontinuation of warfarin preoperatively. In high risk patients, bridging with low-molecular weight heparin, and then resuming therapy after surgery.^{4,5} In

Low risk patients undergoing elective surgery, warfarin is stopped 5 days preoperatively and the International Normalised Ratio (INR) is checked on the day of surgery.⁶ The most common practice is to restart warfarin together with low molecular heparin as soon as the risk of surgical haemorrhage is considered low, usually 24–48 h postoperatively. There is an expected delay before a therapeutic anticoagulant effect is achieved, typically 5–7 days after restarting warfarin.^{7–9}

Recent publications demonstrated the safety of continuation of anticoagulants perioperatively in patients undergoing elective total knee replacement and cardiac device implantation.^{4,10–12} The interruption of anticoagulants perioperatively could mean that patients would require longer hospital stay until their INR is within the desired range. We hypothesised that patients who had their warfarin continued during the perioperative period would have shorter hospital stay and no significant increase in the risks of surgical complications compared to patients who

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had their warfarin interrupted. To our knowledge, this is the first study to assess the safety of hip arthroplasty surgery in orally anticoagulated patients without interrupting their warfarin therapy.

2. Materials and methods

This was a retrospective review of 20 consecutive patients receiving long-term warfarin (Warfarin group) who underwent primary total hip replacement between 2016 and 2018 with no interruption to warfarin therapy. As a control group, we collected the same data from 20 age and gender matched patients also on long term warfarin but their warfarin was stopped prior to their surgery and restarted postoperatively (Control group). Data was extracted from inpatient medical notes, laboratory results, drug charts, operation notes, and anaesthetic reports. Patients in the control group were operated on by 3 surgeons. The indication for primary total hip replacement was osteoarthritis in all patients involved in this study.

In the warfarin group, warfarin daily maintenance dose was reduced for 2 days preoperatively aiming for an INR of ≤ 2.5 on the day of surgery. The INR is checked on the morning of surgery and patients with an INR of ≤ 2.5 underwent their planned procedure. Patients were given their routine warfarin daily dose postoperatively following an INR check (12–24 h postoperatively). Prophylactic dose of low molecular weight heparin (Enoxaparin 40 mg subcutaneously) was also given until INR ≥ 2.0 .

In the control group, warfarin was stopped 5 days preoperatively, INR checked on the morning of surgery and patients underwent surgery if INR was ≤ 1.5 .¹³ All patients in the control group were assessed preoperatively for the risk of venous thromboembolism and were found to have low risk, hence no bridging therapy started. Postoperatively, patients were started on a prophylactic dose of low molecular dose (Enoxaparin 40 mg subcutaneously) and warfarin restarted 48 h after surgery. Low molecular weight heparin was stopped when INR was within therapeutic range. All patients were routinely prescribed mechanical prophylaxis for deep vein thrombosis unless contraindicated.

Patients received either general or spinal anaesthetic and Tranexamic acid on induction. Total hip replacement was performed via a posterior approach with meticulous haemostasis. Local anaesthetic infiltration of the soft tissues and the hip capsule was performed in all patients to help with postoperative analgesia and reduced the need for opioid analgesia. All surgical wounds were closed in a watertight subcuticular Monocryl suture. A second dose of Tranexamic acid (1 g) was given to all patients 8 h postoperatively. All patients were allowed to full weight bear immediately post-operatively and a standardised physiotherapy rehabilitation protocol started on the first postoperative day. Postoperative blood transfusion was based on the National Institute for Health and Care Excellence (NICE) transfusion guidelines depending on the volume of the blood loss, fluid status, haemoglobin (Hb) concentration and the patient's clinical condition.¹⁴ Patients who were symptomatically anaemic with Hb of < 80 were transfused red blood cells and their Hb rechecked. Table (1) shows the characteristics of the two groups of patients.

3. Statistical analysis

Statistical analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois) and Microsoft Excel 2016 (Microsoft, Redmond, WA, USA). Statistical significance was set at $p < 0.05$. Linear variables were summarised by the mean, standard deviation (SD), median and 95% confidence interval (CI). Linear variables were assessed for change over time using the Wilcoxon signed-rank test. The differences between the two groups were examined using the Mann-Witney *U* test. The null hypothesis for the Wilcoxon test is that there is no difference between the two groups.

4. Results

4.1. Patient characteristics

A total of 40 patients on long term warfarin anticoagulation were included in this retrospective study. Of these patients, 20 underwent their planned total hip replacement without discontinuing warfarin preoperatively but slightly reducing the daily dose 2 days preoperatively (Warfarin group). The control group included 20 patients with their warfarin temporarily stopped preoperatively and restarted 48 h after their hip replacement surgery.

The mean ages of patients were 79.05 and 78.13 years in the warfarin group and control groups respectively. Table (2) is a summary of the indications for warfarin therapy in both groups. The main results of this study are summarised in Table (1).

4.1.1. Comorbidities

There was no statistically significant difference in age, BMI or comorbidities between the 2 groups. Table (3) is a summary of comorbidities encountered in both groups.

4.2. International Normalised Ratio (INR)

In the warfarin group the mean preoperative INR was 1.85 (SD 0.245, range; 1.5–2.4) and the mean INR on postoperative day 1 was 1.99 (SD 0.375, range; 1.4–2.7). The mean preoperative and day 1 postoperative INR in the control group were 1.23 (SD 0.156, range; 1–1.6) and 1.41 (SD 0.32, range; 1–2.3) respectively. There was a statistically significant difference between the two groups in the preoperative INR ($P < 0.0001$) and the postoperative INR ($P < 0.0001$). We have also calculated the mean INR for postoperative day 4 for the 2 groups. The mean INR for postop day 4 was 2.23 (SD 0.04, range; 1.9–2.7) for the warfarin group and 1.72 (SD 0.26, range; 1.4–2.3) for the control group. The difference was also statistically significant ($P < 0.0001$). Figures (1&2) are box plots showing the mean and 95% confidence interval for the daily INR for the both groups.

4.3. Haemoglobin (Hb)

In the warfarin group the mean preoperative haemoglobin was 134.7 g/L (SD 8.93, range; 117–157) and the mean postoperative haemoglobin was 117.1 g/L (SD 9.74, range; 95–137). In the control group the mean preoperative haemoglobin was 134.4 g/L (SD 13.39, range; 98–152) and the mean postoperative Hb was 108.3 g/L (SD 14.7, range; 73–128). In this study, the drop in haemoglobin (difference between the pre and postoperative haemoglobin levels) has been calculated as an indirect measure of blood loss. The mean drop in Hb postoperatively was 25.95 g/L in the warfarin group (SD 2.51, range; 5–48) and 35.7 g/L in the control group (SD 14.94, range; 7–57) which was statistically significant ($P = 0.0066$). 95% CIs for pre and post op Hb for both groups is shown in figure (3).

4.4. Blood transfusion

There was no difference between the two groups with regards to the preoperative Hb levels ($P = 0.934$). Four patients in the warfarin group required postoperative blood transfusion compared to five patients in the control group. The difference between the 2 groups was not statistically significant ($P = 0.353$). Table (4) shows the rates of blood transfusion in the two groups.

4.5. Hospital stay

In the warfarin group the mean hospital stay was 4.8 days (SD 2.14, range; 2–9), while in the control group the mean hospital stay was 6.1 days (SD 1.80, range; 3–9). This was statistically significant with a

Table 1
Summary of patient demographics, main study results, and complications encountered.

		Warfarin group	Control group	P Value
Demographics	Number of patients	20	20	
	Males	12	11	
	Mean age	79.3	78.05	
	Mean BMI	29	28.08	
Results	Mean age	79.3	78.05	0.255
	Mean Hospital stay	4.8	6.1	< 0.0001
	Mean Follow up in days	293.4	298.85	0.63
	Mean Preop INR	1.852	1.2315	< 0.0001
	Mean Postop INR	1.99	1.41	< 0.0001
	Mean Preop Hb	134.7	134.4	0.934
	Mean Postop Hb	117.1	108.3	0.0316
	Mean drop in Hb postop day 1	25.95	35.7	0.0066
Complications	Number of patients who received postop blood transfusion	4	5	0.353
	Wound ooze	2	1	
	Superficial wound infection	1	0	
	Deep vein thrombosis (DVT)	0	1	
	Pulmonary embolism (PE)	0	0	
	Total	3	2	

Table 2
Indication of warfarin in warfarin group.

Indication for Warfarin	Number of patients
Atrial Fibrillation	14
History of deep vein thrombosis	3
History of pulmonary embolism	2
History of transient ischaemic attack	2
History of mechanical heart valve	1

Table 3
Summary of comorbidities encountered in both groups.

Comorbidities	Warfarin group	Control group
Hypertension	8	9
Diabetes Mellitus	2	1
Atrial Fibrillation	14	2
Fibromyalgia	3	2

mean shorter hospital stay observed in the warfarin group ($P = 0.0447$).

4.6. Postoperative complications

In the warfarin group, 2 patients had postoperative serosanguinous wound ooze managed with change of dressings, and 1 patient had superficial wound infection and was treated with a course of oral antibiotics. In the control group, 1 patient had serosanguinous wound ooze managed conservatively and 1 patient had a swollen ipsilateral calf with deep vein thrombosis (DVT) confirmed with a Doppler ultrasound scan. The odds ratio for developing a postoperative complication was 1.5882 (95% CI 0.23–10.70) which was not statistically significant ($P = 0.6346$). Table (1) shows incidence of postoperative complications.

5. Discussion

To our knowledge, this is the first study to assess the safety of continuation of warfarin therapy in patients undergoing elective total hip replacement. The study compared two different strategies in managing warfarin perioperatively. The consensus guideline in low risk patients is to stop warfarin 5 days preoperatively with postoperative bridging to warfarin 48 h postoperatively.⁶ This is mainly to reduce the

Fig. 1. Box plot showing the mean and 95% confidence interval for the daily INR for the warfarin group.

Fig. 2. Box plot showing the mean and 95% confidence interval for the daily INR for the cohort group.

risk of postoperative bleeding and wound complications. The main findings of our study support the continuation of warfarin in patients on long term anticoagulation therapy as it appears to be a safe practice with no significant increase in complications or need for blood transfusion. Discontinuation of warfarin (control group) was associated with longer hospital stay owing to the time required for the INR to reach therapeutic levels.

Recent published studies assessed the safety of continuation of warfarin in knee arthroplasty.^{12,15,16} Chana et al.,¹⁵ Phillips et al.,¹² and Rhodes et al.¹⁶ investigated the continuation of warfarin in patients undergoing total knee arthroplasty and found no increase in the rate of haemorrhage for patients on continuous warfarin. In our study, there was a statistically significant difference ($P < 0.0001$) in INR levels between the warfarin group (1.85 preop, 1.99 day 1, and 2.23 day 4) and the control group (1.23 preop, 1.41 day 1, 1.72 day 4). The control group had significantly larger fluctuations between pre and post-operative INR levels. This would explain the longer hospital stay observed in the control group as it took significantly longer for therapeutic levels of warfarin to be achieved.

In the warfarin group the mean hospital stay was 4.8 days (SD 2.14, range; 2–9), compared to the 6.1 days (SD 1.80, range; 3–9) in the control group. This was statistically significant with shorter hospital

Table 4

Blood transfusion requirements.

Number of packed red blood cell units	Number of patients in Warfarin group	Number of patients in Cohort group
0	16	15
1	1	2
2	2	3
3	1	0

stay observed in the warfarin group ($P = 0.0447$). We found no significant increase in the incidence of postoperative complications in the warfarin group. Chana et al., Rhodes et al., and Phillips et al. also found no statistically significant difference in complication rates.^{12,15,16}

There was no significant increase in blood transfusion requirement observed in the warfarin group. There was also no difference in pre-operative Hb between the two groups and the expectation would be that a larger drop in Hb would be observed in the warfarin group due to the risk of bleeding but this was not the case. With regards to haemoglobin levels, our study showed a statistically significant ($P = 0.0066$) mean drop in Hb postoperatively with larger mean drop in Hb on postoperative day 1 in the control group (35.7 g/L) compared

Fig. 3. Means plot showing the mean daily haemoglobin changes in both groups. The error bars show the standard deviation.

to the warfarin group (25.95 g/L).

Interruption of anticoagulation in patients on chronic warfarin therapy poses a major risk of morbidity and mortality.^{16–18} There is an increased risk of thromboembolism when long term oral anticoagulation is interrupted prior to surgery.^{16,19} Several studies have reported increased thrombin activity after warfarin withdrawal as a result of rebound hypercoagulability.^{15,20,21} In addition to this, achieving a therapeutic INR and restoring the patient to their pre-operative levels is often associated with extended hospital stays and increased costs of treatment.^{15,22,23} There have been several reports of large INR fluctuations during the first few days following surgery.^{15,16} Inconsistent anticoagulation during this time could increase the risk of DVT and PE.^{15,24,25}

5.1. Study limitations

This was a retrospective study with relatively small numbers of patients in each group making the statistics more prone to type II error. Our inability to analyse a larger number of patients does not diminish our continued view that this is a safe approach. Patients in the warfarin group were operated on by one arthroplasty surgeon, however this was not the case for patients in the control group (3 surgeons). Difference in surgical technique, operative time, implants used (cemented or uncemented) may have existed among the studied groups which was not analysed in this study. These limitations should be taken into consideration when interrupting the results of this study.

6. Conclusion

The results of this study support the hypothesis that it is safe to continue warfarin in patients on long term anticoagulation undergoing elective total hip replacement. The continuation of warfarin was associated with significantly shorter hospital stay and less fluctuations in INR levels. There was no significant increase in the risk of complications or blood transfusion. We acknowledge the limitations of this study; however, we believe that our results contribute to the growing body of evidence that supports the continuation of warfarin in patients on long-term anticoagulants undergoing elective arthroplasty surgery. Perhaps a randomised study powered to show a difference between the two strategies could provide a more robust evidence and guidance for clinical practice.

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Conflicts of interest

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jor.2019.06.024>.

References

- Listed NA. *National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. 14th Annual Report 2017*. 2017; 2017.
- Phillips A, Dan M, Schaefer N, Randle R. Warfarin cessation is non-essential in patients undergoing total knee arthroplasty—a case-control study. *J Orthop Surg Res*. 2015;10:16. <https://doi.org/10.1186/s13018-015-0153-4>.
- Chana R, Salmon L, Waller A, Pinczewski L. Warfarin management in patients on continuous anticoagulation therapy undergoing total knee replacement. *The Bone & Joint Journal*. 2011;93-B(11):1497–1502. <https://doi.org/10.1302/0301-620X.93B11.27255>.
- Rhodes DA, Severson EP, Hodrick JT, Dunn HK, Hofmann AA. Discontinuation of warfarin is unnecessary in total knee arthroplasty. *Clinical Orthopaedics and Related Research*. vol. 468. 2010; 2010:120–126. <https://doi.org/10.1007/s11999-009-1128-8>.
- Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. vol. 126. 2004; 2004:https://doi.org/10.1378/chest.126.3_suppl.338S.
- Keeling D, Tait RC, Watson H. The British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. *Br J Haematol*. 2016;175(4):602–613. <https://doi.org/10.1111/bjh.14344>.
- Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. *Blood*. 2012;120(24):4699–4705. <https://doi.org/10.1182/blood-2012-05-423228>.
- Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized peri-procedural anticoagulation regimen. *Arch Intern Med*. 2004;164(12):1319–1326. <https://doi.org/10.1001/archinte.164.12.1319>.
- Kovacs MJ, Kearon C, Rodger M, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation*. 2004;110(12):1658–1663. <https://doi.org/10.1161/01.CIR.0000142859.77578.C9>.
- Jacob AK, Hurley SP, Loughran SM, Wetsch TM, Trousdale RT. Continuing clopidogrel during elective total hip and knee arthroplasty: assessment of bleeding risk and adverse outcomes. *J Arthroplast*. 2014;29(2):325–328. <https://doi.org/10.1016/j.arth.2013.06.008>.
- Madan S, Muthusamy P, Mowers KL, et al. Safety of anticoagulation with uninterrupted warfarin vs. interrupted dabigatran in patients requiring an implantable cardiac device. *Cardiovasc Diagn Ther*. 2016;6(1):3–9. <https://doi.org/10.3978/j.issn.2223-3652.2015.10.06>.
- Phillips A, Dan M, Schaefer N, Randle R. Warfarin cessation is non-essential in patients undergoing total knee arthroplasty—a case-control study. *J Orthop Surg Res*. 2015;10:16. <https://doi.org/10.1186/s13018-015-0153-4>.
- Keeling D, Tait RC, Watson H, British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. *Br J Haematol*. 2016;175(4):602–613. <https://doi.org/10.1111/bjh.14344>.
- Transfuse and Check' – improving post-operative blood transfusion in line with NICE guidance. NICE. <https://www.nice.org.uk/sharedlearning/transfuse-and-check-improving-post-operative-blood-transfusion-in-line-with-nice-guidance>, Accessed date: 15 October 2018 Accessed '.
- Chana R, Salmon L, Waller A, Pinczewski L. Warfarin management in patients on continuous anticoagulation therapy undergoing total knee replacement. *J Bone Joint Surg Br*. 2011;93(11):1497–1502. <https://doi.org/10.1302/0301-620X.93B11.27255>.
- Rhodes DA, Severson EP, Hodrick JT, Dunn HK, Hofmann AA. Discontinuation of warfarin is unnecessary in total knee arthroplasty. *Clin Orthop Relat Res*. 2010;468(1):120–126. <https://doi.org/10.1007/s11999-009-1128-8>.
- Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med*. 1997;336(21):1506–1511. <https://doi.org/10.1056/NEJM199705223362107>.
- Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Research Committee of the British Thoracic Society. *Lancet*. 1992;340(8824):873–876.
- Blacker DJ, Wijndicks EFM, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology*. 2003;61(7):964–968.
- Poller L, Thomson J. EVIDENCE FOR “REBOUND” HYPERCOAGULABILITY AFTER STOPPING ANTICOAGULANTS. *Lancet*. 1964;2(7350):62–64.
- Genewein U, Haerberli A, Straub PW, Beer JH. Rebound after cessation of oral anticoagulant therapy: the biochemical evidence. *Br J Haematol*. 1996;92(2):479–485.
- Carter G, Goss A. Tranexamic acid mouthwash—a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg*. 2003;32(5):504–507.
- McLemore EC, Harold KL, Cha SS, Johnson DJ, Fowl RJ. The safety of open inguinal herniorrhaphy in patients on chronic warfarin therapy. - PubMed - NCBI. Published 192:860–864 2006. Accessed <https://www.ncbi.nlm.nih.gov/pubmed/?term=The+safety+of+open+inguinal+herniorrhaphy+in+patients+on+chronic+warfarin+therapy>, Accessed date: 1 November 2018.
- Pelligrini V, Donaldson C, Farber D. The Mark Coventry Award: prevention of readmission for venous thromboembolism after total knee arthroplasty. - PubMed - NCBI. <https://www.ncbi.nlm.nih.gov/pubmed/16906107>, Accessed date: 1 November 2018 Accessed.
- Leiberman JR, Wollaefer J, Dorey F, et al. The efficacy of prophylaxis with low-dose warfarin for prevention of pulmonary embolism following total hip arthroplasty. - PubMed - NCBI. <https://www.ncbi.nlm.nih.gov/pubmed/9070518>, Accessed date: 1 November 2018 Accessed.