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ORIGINAL ARTICLE

Warfarin should not be used for thromboprohylaxis in elective major orthopaedic surgery: a Croatian perspective

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ABSTRACT

Aim To identify modes of venous thromboembolism (VTE) prophylaxis in patients undergoing elective major orthopaedic surgery (total hip or knee arthroplasty, THA/TKA) at a single university-associated hospital in Croatia.

Methods A retrospective analysis of consecutive patients subjected to THA or TKA over a two-year period (2014-2015) with a focus on anticoagulation during the first 15 post-surgical days (period of highest VTE risk).

Results Of 603 identified patients three (0.5%) were not anticoagulated (haemophilia) and others received perioperative doses of low molecular weight heparins (LMWH). Overall, 228 (37.8%) patients received prophylaxis not involving warfarin, and 372 continued with short-term LMWH with switching to warfarin. They contributed a total of 1218 international normalized ratio (INR) values (median=3, range=1-8). These were consistently below the target INR range across the observed period. Between post-surgical days 6 and 15 (after the initial titration), 438 values were taken in patients treated with LMWH+warfarin and 92.7% were below, and only 6.8% within the target range; 580 values were taken in patients already switched to warfarin, 74% were below and only 25% within the range.

Conclusion The prevailing mode of VTE prophylaxis was in a clear contrast to (then) actual professional guidelines, with inadequate monitoring and poor anticoagulation. There is no reason to expect a substantially different situation at other institutions across the country. The prevailing practice of VTE prophylaxis in major orthopaedic surgery in Croatia should be promptly abandoned and up-dated in agreement with the current state of the art.

Key words: hip, knee, arthroplasty, venous thromboembolism

INTRODUCTION

Elective total hip (THA) and knee arthroplasty (TKA) are highly successful procedures that convey great improvements in functional ability and quality of life in patients suffering a variety of pathological hip/knee conditions. Both surgeries have a successful and long-standing history in Croatia (1). However, both procedures are associated with an increased risk of post-surgical venous thromboembolic incidents (VTE) – deep venous thrombosis or pulmonary embolism. In the 1970s, the estimated risk of such events was in the range of 20-25% but introduction of thromboprophylaxis, improvement of surgical techniques and post-surgical management (e.g., early ambulation) have greatly reduced their occurrence (2). As estimated by the American College of Chest Physicians (ACCP), the critical period for the occurrence of VTE lasts for 30-35 post-surgical days and a contemporary risk of symptomatic VTE associated with elective THA/TKA without prophylaxis is estimated at 2.9% over the first 15 post-surgical days and up to 4.6% during the 30-35 days (2). While there are different mechanical and pharmacological means of thromboprophylaxis, a thorough systematic review conducted by ACCP demonstrated that pharmacological means should be preferred except when explicitly contraindicated (2). Based on a comprehensive evaluation of clinical trial data of individual pharmacological means vs. no treatment, mechanical methods or vs. each other, which assessed the risk of VTE and the risk of relevant bleedings (i.e., major or non-major clinically relevant), ACCP also suggested that low-dose acetylsalicylic acid (alone or combined with mechanical means) and unfractionated heparin should not be used in this setting, emphasized the role of low molecular weight heparins (LMWH) particularly in comparison to vitamin K antagonists and depicted the emerging role of the new orally active anticoagulants (NOACs) (2).

There are no formal surveys on thrombophrophylaxis in this setting in Croatia, but an *ad hoc* survey among the members of the Croatian Orthopaedic Society during the 2016 annual assembly confirmed the common knowledge - the prevailing mode of thrombophrophylaxis related to THA/TKA consists of a short-term peri-operative (up to several days after the surgery) use of LMWH (first dose before the surgery) with concomitant introduction of vitamin K antagonists (almost exclusively warfarin) and subsequent continuation of treatment with warfarin, and is driven by the policy of the Croatian Health Insurance fund which reimburses only the "in-hospital" use of LMWH. However, ACCP has demonstrated (2) that even under the conditions of controlled clinical trials with extremely high rate of appropriate warfarin use (time in therapeutic range, TTR), i.e. with international normalized ratio (INR) values between 2.0 and 3.0 (targeted value 2.5%), >60%), this strategy was inferior to the exclusive use of LMWH as it resulted in several excess cases of VTE and 40 excess cases of major bleeding/1000 treated.

An observational study in the USA (2009-2011) included 596 THA/TKA patients treated with such an approach, who received warfarin over 10-35 days and were monitored through specialized anticoagulation clinics at two university hospitals (3). The average TTR was 36% and median time to the first INR within the target range was 12-13 days. A similar study (4) embraced 3313 THA/TKA patients (2005-2009). The median number of determined INR values over the 28-35 post-surgical days per patient was 5 (excluded were the initial 5 days of "early titration"). The average TTR was 28%, only 33% of the determined INR values were within the range, average proportion of time with INR <2.0 was 64%, and patients who did not experience a single INR value within the range had 5.3 times higher risk of symptomatic VTE (incidence of VTE in the cohort was 3.3%). Overall, data suggest that even with stringent monitoring and careful titration, warfarin does not seem to achieve the desired level of anticoagulant activity during the period of the highest VTE risk.

Warfarin-based anticoagulation is specific in that it successfulness greatly depends on close monitoring. There are no specialized anticoagulation clinics in Croatia and no structured monitoring systems (e.g., registries) of long-term anticoagulation e.g. in stroke prevention or VTE treatment/prophylaxis. A recent study demonstrated a poor practice of warfarin-based anticoagulation in Croatian patients with atrial fibrillation scheduled for direct current cardioversion (5). The present analysis aimed to evaluate anticoagulation adequacy in elective major orthopaedic surgery in a specialized Croatian hospital.

PATIENTS AND METHODS

Study design

This retrospective analysis refers to a 2-year period (January 1 2014 – December 31 2015) at the Department of Trauma Surgery, University Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia in order to identify modes of venous thromboembolism (VTE) prophylaxis in patients undergoing elective major orthopaedic surgery (total hip or knee arthroplasty, THA/TKA).

The study was approved by the Ethics Committee of the University Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia.

Eligible for inclusion were consecutive patients who underwent primary elective THA/TKA.

Methods

Two researches independently searched the hospital electronic database system for the specific procedure codes matched with the unique patient identification numbers. Results were mutually re-checked and verified through hard-copy archives. Demographic, comorbidity, co-medication data and data on peri-operative anticoagulation treatment, as well as laboratory data on coagulation monitoring tests were extracted for a period of 15 post-surgical days (Table 1). We restricted the observational period to the first 15 post-surgical days as this is the period of the highest risk for VTE.

RESULTS

A total of 603 patients were enrolled, mostly subjected to THA, 434 (72%) (Table 1).

Table 1. Characteristics of patients who underwent elective major orthopaedic surgery (total hip or knee arthroplasty)

Characteristic	No (%) of patients
Total	603
Total hip / knee arthroplasty	434 (72) / 169
Age (range, years)	69 (20-97)
Males	273 (45.3)
Previous use of antiplatelet	76 (12.6)
Previous use of anticoagulants	33 (5.4)
History of pulmonary embolism	1 (0.2)
History of deep venous thrombosis	20 (3.3)
History of myocardial infarction or angina	23 (3.8)
History of transitory ischemic attack or stroke	10 (1.7)
Atrial fibrillation or flutter	25 (4.1)
Chronic heart failure	71 (11.8)
Venous insufficiency	50 (8.3)
Diabetes mellitus	71 (11.8)
Thrombocytopenia	6 (1.0)
Haemophilia	3 (0.5)

Apart from three patients with haemophilia, all underwent anticoagulation and received a pre-surgical and a post-surgical low molecular weight heparin (LMWH) dose (Figure 1). For 228 (37.8%) patients anticoagulation did not include warfarin, however for 120 (19.9%) patients only short-term LMWH treatment could be verified without any information about further prophylaxis. Overall 103 (17.1%) patients received LMWH prophylaxis during the observed period, and sporadic patients were treated with new orally active anticoagulants (NOACs) or LMWH, and acetylsalicylic acid. The majority of the patients, 372 (61.5%) underwent prophylaxis with LMWH switching to warfarin and contributed a total of 1218 INR values (median=3, range 1-8 per patient). Almost 1/3 one third of the patients, 113 (30.4%) contributed only 1 or 2 INR values over the observed 15 days (Figure 1).
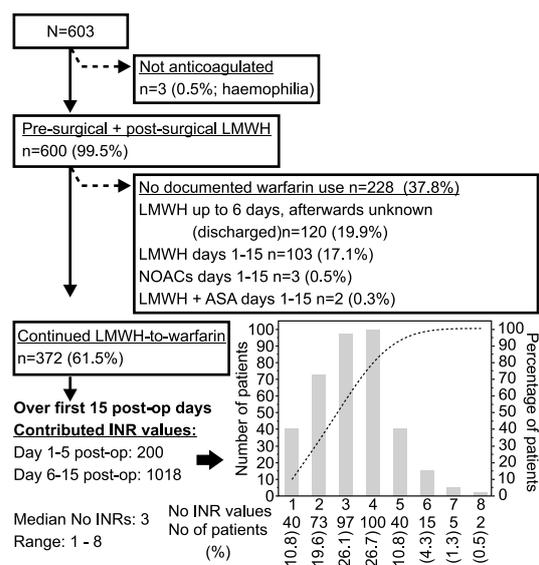

Figure 1. Patient eligibility diagram. Histogram depicts distribution of patients (absolute counts and cumulative relative distribution) across the number of contributed international normalized ratio (INR) values
ASA, acetylsalicylic acid; LMWH, low molecular weight heparin; NOACs, new orally active anticoagulants

Regardless of the treatment under which INR values were provided, over time they were consistently below the target INR range. Considering the period between days 6-15 (after initial titration would be expected to be accomplished), 92.7% out of 439 values taken in patients under LMWH + warfarin treatment were below the target as well as 74% out of 580 values taken in
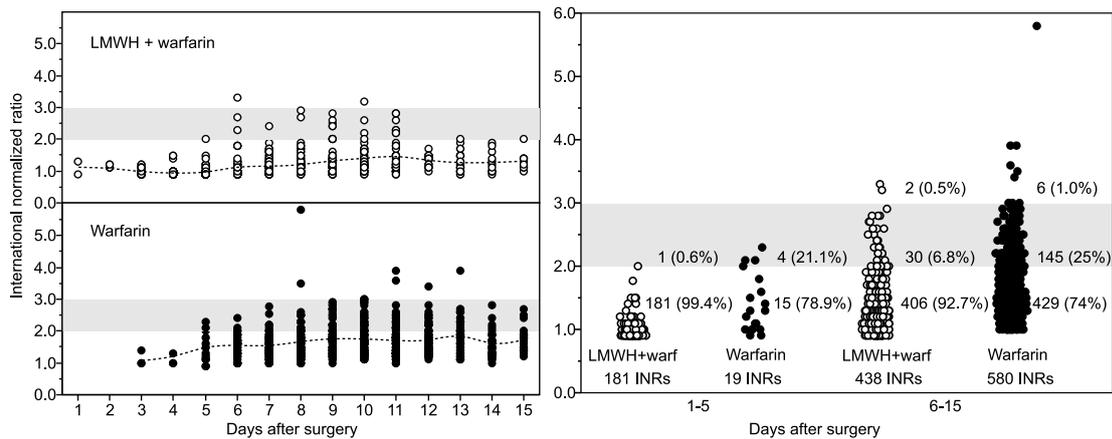
Figure 2. International normalized ratio (INR) values in the subset of patients anticoagulated by the "LMWH-to-warfarin" treatment. Shaded areas indicate the target INR range. Individual values (circles) across the observed 15 days by treatment (left) and individual values at days 1-5 and 6-15 by treatment (right) with the absolute number (percentage) of values below, within and above the range
LMWH, low molecular weight heparin; Warf, warfarin

patients already switched to warfarin, with only 25% within the target range (Figure 2).

DISCUSSION

Although conducted at a single centre and thus not representative for the entire country, the present results confirmed three expectations. First, the initial use of LMWH with switching to warfarin was the most predominant practice. Second, in the setting of major orthopaedic surgery there was no "centralized structured" monitoring of successfulness of anticoagulation: at the institution at which the surgery was indicated and performed, and at which the anticoagulation was initiated, only sparse data on a laboratory marker (i.e., INR in patients treated with warfarin) of its successfulness were recorded (30.4% patients contributed only 1 or 2 INR values over the observed period) and there were practically no records on the overall outcome (i.e., records of VTE/bleedings during the first month post-surgery). Third, although TTR could not be determined due to paucity of the international normalized ratio (INR) values, data on percentage of values within the target INR range, particularly those taken between days 6 and 15 (after the "initial titration" period) strongly indicate the failure of the procedure to achieve a known strongly predictive (for clinical outcomes) laboratory goal during the period of the highest VTE risk. While patients treated with both LMWH and warfarin could be considered "protected" (on the account of LMWH), the fact that 92.7% of their INR va-

lues were below the target clearly demonstrated that they were not fit to continue only warfarin treatment. On the other hand, the fact that 74% of the values taken in patients treated with warfarin were only below the target clearly documented excessive "under-protection" from the VTE risk.

In 2012 the American College of Chest Physicians (ACCP) clearly recommended the preference of pharmacological over mechanical (various forms) thromboprophylaxis in major orthopaedic surgery (except where the former were explicitly contraindicated) and strongly advised (based on randomized controlled trial data) against the use of vitamin K antagonists (e.g., warfarin) due to inferior balance between the VTE and bleeding risks as compared to LMWH (2). Observational data with stringent anticoagulation monitoring (3,4) demonstrated that warfarin inherently did not seem to be appropriate for a setting in which a rapid onset of a relative short anticoagulation is needed (30 days overall, with the highest risk over first 15 post-surgical days): median time to target INR has been estimated to equal the period of the highest risk (12-13 days) (3), time in therapeutic range over the first 30 post-surgical days has been repeatedly reported to be around 30% (3,4) with around 30% of INR values within the range (4). The present data are in line with these observations and actually indicate that the situation is even worse when there is no structured monitoring of the warfarin effect. In one large cohort (3313 THA/TKA patients) treated with warfarin between post-sur-

gical days 5-30 (4), the rate of symptomatic VTE was 3.3% - almost as if no anticoagulation was installed: the best estimate of the contemporary VTE risk without thromboprophylaxis is 4.6% (cumulatively over 30-35 days) and appropriate prophylaxis is expected to reduce it by 65-70%, relatively (2). Clearly, it is time to completely abandon the practice of warfarin use in this setting. In 2012, ACCP recommended the use of LMWH (during the entire period of the increased risk) (2). In the meantime, NOACs have emerged as a new valid option: three have gained regulatory approval in this setting (dabigatran, rivaroxaban, apixaban) and have demonstrated a comparable VTE/bleeding risks balance as compared to LMWH (6,7) with a convenience of simpler oral dosing. Nowadays, therefore, the most adequate options for VTE prophylaxis in major orthopaedic surgery should be identified among LMWH and NOACs and should take into account not only population estimates of their efficacy and safety, but also individual pharmacological characteristics (e.g., pharmacokinetics, dependence on renal function) and co-morbidity (e.g. existing long-term antico-agulation due to non-valvular atrial fibrillation or long-term VTE prophylaxis for other reasons) in order to apply the optimum choice for each individual patient.

In conclusion, the presented insight into thromboprophylaxis in major orthopaedic surgery at a single university-affiliated centre in Croatia disclosed that the prevailing mode of VTE prophylaxis was in clear contrast to (then) actual professional guidelines, with inadequate monitoring and poor anticoagulation. There is no reason to expect a substantially different situation in other institutions across the country. The prevailing practice of VTE prophylaxis in major orthopaedic surgery in Croatia should be promptly abandoned and up-dated in agreement with the current state of the art.

FUNDING

TRANSPARENCY DECLARATION

Conflicts of interest: none to declare

REFERENCES

1. Kolundžić R, Orlić D. Forty years of total hip replacement in Croatia at the department of orthopedic surgery Zagreb – orthopedic surgery of the 20th century. Lijec Vjesn 2011; 133:343-51.
2. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr; American College of Chest Physicians. Prevention of VTE in orthopedic surgery patients. Antithrombotic therapy and prevention of thrombosis 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(suppl):e278S-e325S.
3. Barnes GD, Kaatz S, Golgotiu V, Gu X, Leidal A, Kobeissy A, Haymart B, Kline-Rogers E, Kozlowski J, Almany S, Leyden T, Froehlich JB. Use of warfarin for venous thromboembolism prophylaxis following knee and hip arthroplasty: results of the Michigan Anticoagulation Quality Improvement Initiative (MAQI2). J Thromb Thrombolysis 2013; 35:10-4.
4. Nordstrom BL, Kachroo S, Fraeman KH. Warfarin prophylaxis in patients after total knee or hip arthroplasty – international normalized ratio patterns and venous thromboembolism. Curr Med Res Opinion 2011; 27:1973-85.
5. Dubravčić M, Cukon P, Car S, Puljević D, Trkulja V. Croatia needs a registry of patients undergoing direct current cardioversion for persistent atrial fibrillation/flutter. Croat Med J 2016; 31:403-5.
6. Trkulja V. Safety of apixaban for venous thromboembolism prophylaxis: the evidence to date. Drug Health Patient Saf 2016; 19:25-38.
7. Trkulja V, Kolundžić R. Rivaroxaban vs. dabigatran for thromboprophylaxis after joint-replacement surgery: exploratory indirect comparison based on meta-analysis of pivotal clinical trials. Croat Med J 2010; 51:113-23.

U tromboprofilaksi u bolesnika podvrgnutih elektivnim velikim ortopedskim zahvatima ne bi trebalo korisiti varfarin: iskustvo iz Hrvatske

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SAŽETAK

Cilj Identificirati modalitete prevencije venskog tromboembolizma (VTE) u bolesnika podvrgnutih elektivnim velikim ortopedskim zahvatima (totalna artroplastika kuka ili koljena) u jednom sveučilišnom medicinskom centru u Hrvatskoj.

Metode Retrospektivna analiza podataka o uzastopnim bolesnicima, podvrgnutim totalnoj artroplastici kuka ili koljena, tijekom dvije godine (2014-2015), s fokusom na antikoagulacijsko liječenje tijekom prvih 15 postoperativnih dana (razdoblje najvišeg rizika za VTE).

Rezultati Od ukupno 603 bolesnika, troje (0.5%) nisu bili antikoagulirani (hemofilija), dok su ostali primili preoperativne doze niskomolekularnog heparina (LMWH). U ukupno 228 (37.8%) bolesnika antikoagulacijski tretman nije uključivao varfarin, dok su 372 bolesnika tretirana kratkotrajnom primjenom LMWH-a s prijelazom na varfarin. Tijekom promatranog razdoblja ukupno je izmjereno 1.218 vrijednosti internacionalnog normaliziranog omjera (INR) (medijan=3, raspon= 1-8, po bolesniku). Vrijednosti su konzistentno bile ispod terapijskog INR-raspona. U razdoblju između šestog i petnaestog postoperativnog dana (nakon početne titracije), ukupno je izmjereno 438 INR-vrijednosti u bolesnika koji su primali i LMWH i varfarin, te je 92.7% njih bilo ispod terapijskog raspona, a samo 6.8% vrijednosti bilo je u terapijskom rasponu. Istodobno, izmjereno je ukupno 580 INR-vrijednosti u bolesnika koji su već bili prebačeni na varfarin – 74% vrijednosti bilo je ispod, a samo 25% vrijednosti bilo je u terapijskom rasponu.

Zaključak Opaženi dominantni oblik VTE profilakse u izravnoj je suprotnosti s profesionalnim smjernicama, s neadekvatnim nadzorom i nedostatnom antikoagulacijom. Nema razloga očekivati da je stanje bitno drugačije u ostalim institucijama u zemlji. Taj predominantni oblik VTE profilakse u velikim ortopedskim zahvatima u Hrvatskoj treba što prije napustiti i uvesti postupke u skladu s trenutno važećim standardima dobre kliničke prakse.

Ključne riječi kuk, koljeno, artroplastika, venski tromboembolizam