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Review Article

Effect of influenza vaccination on international normalized ratio during chronic warfarin therapy

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ABSTRACT

What is known and Objective: **Warfarin is a widely used anticoagulant, well-known for its interactions with medications and foods. Vaccinations, particularly the influenza vaccine, have been thought to potentially interfere with anticoagulation response in those on chronic warfarin. Our objective was to systematically review the literature to assess the validity and clinical significance of this association.**
Methods: **A primary literature search was performed using MEDLINE (1966 – June 2011) and EMBASE (1980 – June 2011). Additional studies were obtained by performing a manual bibliographical review of literature from the initial results and by searching The Cochrane Database of Systematic Reviews. All English-language, peer-reviewed publications identified were evaluated. Reviews, case studies and trials reporting anticoagulation response using an unconverted prothrombin time ratio were excluded.**
Results and Discussion: **Thirty-one abstracts were initially reviewed, and seven studies were identified for inclusion in this review. Significant changes in mean INR post-vaccination between the study and comparator groups were documented in one trial. Through subgroup analysis, another study noted that elderly patients spent more time in the subtherapeutic range post-vaccination when compared with baseline INR levels. No other significant changes in mean INR levels were documented following influenza vaccination. Adverse bleeding events reported after immunization were limited and minor in nature.**
What is new and Conclusion: **Overall, our review does not indicate a consistent, clinically relevant effect of influenza vaccines on INR of patients on chronic warfarin therapy. Isolated reports of variations in INR following influenza vaccination are likely due to other factors.**

WHAT IS KNOWN AND OBJECTIVE

For the past several decades, warfarin sodium has been a mainstay of anticoagulation therapy for millions of patients in the treatment and prophylaxis of various thrombotic events.[1,2] While effective, the vitamin K antagonist has a narrow therapeutic range.[1] Thus, patients receiving warfarin require regular monitoring for adverse events and are assessed for anticoagulation response via a standardized measurement of prothrombin time (PT), or international normalized ratio (INR). Several factors may cause INR to fluctuate, and interactions that result from interferences in hepatic metabolism of warfarin or disruptions in systemic vitamin K levels are two of the most common mechanisms.[2] Several foods and medications are known to significantly interact with warfarin in this manner. More recently, studies have suggested that vaccines may also potentially affect INR through similar means.[3,4]

In 1984, an index case study by Kramer *et al.*[5] described an 81-year-old patient who experienced a gastrointestinal bleed 10 days after receiving an inactivated influenza vaccine while on chronic warfarin therapy. As the patient was previously stable on warfarin, the cause of the bleed was attributed to the influenza vaccine. Two studies, also led by Kramer,[3,5] appeared to support this association. In the first study, an increase in anticoagulant effect was observed when the influenza vaccine was administered, but warfarin's serum level was not affected.[5] In the second study, metabolism of warfarin decreased after inoculation of healthy patients.[3] Based on the case report and the two studies, the authors concluded that the increased anticoagulant response is related to procoagulant synthesis rather than an alteration in warfarin metabolism and serum concentration.[3,5] Since the publication of the index case, several additional studies have been conducted to evaluate the effect of influenza vaccination on PT in individuals on long-term warfarin (Table 1).[6–11] Overall, the results do not support the association made by Kramer *et al.* as no clinically significant, if any, increase in PT was documented.[5–11] However, most of these studies were small and had insufficient statistical power to exclude the possibility that such an effect might be seen in some patients.[12] In addition, differences in the tissue factor used to perform the PT measurement make interpretation of the results difficult.[13] As a result, the effect of influenza vaccination on anticoagulation remains controversial as reflected in the 2004 and 2008 CHEST guidelines, which vacillate between classifying the influenza vaccine as an agent that potentiates (2004) or inhibits (2008) warfarin.[1,14]

Since millions of seasonal influenza vaccinations are given each year, the possibility that the influenza vaccine might affect warfarin anticoagulation response is concerning.[15] Our objective

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Table 1. Summary of studies evaluating the effect of influenza vaccine on prothrombin time (PT)

Study design	Study pts. (*N*)	Results/comments
Prospective[6]	21	For days 2–15 post-vaccination, no significant change in mean PT values compared with baseline and the 3 months prior to vaccination; no bleeding, thrombotic, or embolic problems were reported within the month post-vaccine
Prospective[7]	Year 1 = 7; Year 2 = 12	No change in PT observed following vaccination for both years; no bleeding events noted
Prospective, case–controlled[8]	16 (seven patients receiving warfarin; nine control)	No significant difference in mean PT values (weeks 1, 3, and 5) post-vaccination com pared with pre-vaccination; bleeding was not observed
Prospective[9]	12	Small but significant increase in PT ratio (7·6%) was observed; maximal increase occurred on day 14; no bleeding or thrombotic events were noted
Prospective[10]	24	No statistically significant increase in PT; a statistically significant decrease in PT during the first 2 weeks post-vaccination ($P < 0·05$) was documented; minor complications including nosebleeds and bruising occurred in two patients prior to vaccination and three patients post-vaccination
Prospective[11]	41	No significant change in PT between baseline and days 3, 7, and 14 days post-vaccination; no bleeding episodes were observed

was to systematically review the literature to better assess the validity and clinical significance of this association.

METHODS

A literature search was conducted using MEDLINE (1966 – June 2011) and EMBASE (1980 – June 2011) using combinations of the following terms: influenza vaccine, warfarin, interaction, anticoagulation and INR. Studies were limited to trials evaluating INR as the outcome. The search was restricted to studies conducted in humans and published in English. Additional studies were obtained by performing a manual bibliographic review of literature from the initial results and by searching The Cochrane Database of Systematic Reviews. Reviews, case studies and trials reporting anticoagulation response using an unconverted PT ratio were excluded. Abstracts and articles were reviewed for relevance by each author independently.

RESULTS AND DISCUSSION

Thirty-one abstracts were reviewed and critiqued by each author independently. Twenty-four abstracts were excluded because the inclusion criteria were not met (Fig. 1), leaving seven studies for inclusion (Table 2).[16–22]

Retrospective studies

Jackson *et al.*[19] conducted a large, retrospective cohort study in which patients were included if they were stable on warfarin therapy as defined by at least three INR levels within therapeutic range (≥2 to ≤4) for at least three consecutive months and received any one of four vaccinations between the years 1992 and 2003. Of the 4923 patients who received a trivalent, inactivated influenza vaccination, mean INR values 28 days following influenza vaccination did not differ significantly from mean values outside of the 28-day post-vaccination period even after adjusting for potential confounders (2·53 vs. 2·54 respectively; mean INR difference 0·01; 95% CI −0·01 to 0·03). No safety parameters were evaluated as part of this study.

Prospective studies – uncontrolled

MacCallum *et al.*[16] conducted an audit of 78 patients receiving long-term warfarin therapy who reported receiving an influenza vaccine within 10 days prior to a clinic visit. To reduce the influence of intrapatient variability on INR levels, post-vaccination INR levels were standardized against patient-specific INR data within 1 year of the study vaccination date. Comparable patterns of variability were noticed between outlying INR values post-vaccination and similar outliers independent of influenza vaccination. The study also plotted standardized INR values for each patient between days 1 and 10 post-vaccination. The influenza vaccine had no effect on INR because any variation was not dependent on time elapsed from vaccination. None of the patients reported experiencing any adverse bleeding or thrombotic events.

In a study by Arnold *et al.*,[22] changes in INR following influenza vaccination were assessed in nine patients who were on a stable dose of warfarin for at least 2 months prior to study enrollment. Following influenza vaccination, patient INRs were assessed at seven different time points over the course of 30 days. Median INRs following vaccination were not significantly different from median baseline INR values. One patient experienced epistaxis during the final week of the study, and it was noted that the patient's INR during this time was lower than at baseline.

Prospective studies – case controlled

Ninety patients considered stable on anticoagulant therapy for 3 months prior to study inclusion were assessed by Paliani *et al.*[17] Ninety-eight percent of these patients received warfarin, while 2% received acenocourmarol. Patient INR values were assessed three times prior to influenza vaccination against a matched comparator group, with the values taken 5–7 days before immunization and 7–10 days post-vaccination. At study completion, the study group had an increase in mean INR of 0·56 from baseline. The difference between mean INR in the two groups was considered significant (3·35 ± 1·04 study vs. 2·59 ± 0·90 comparator,

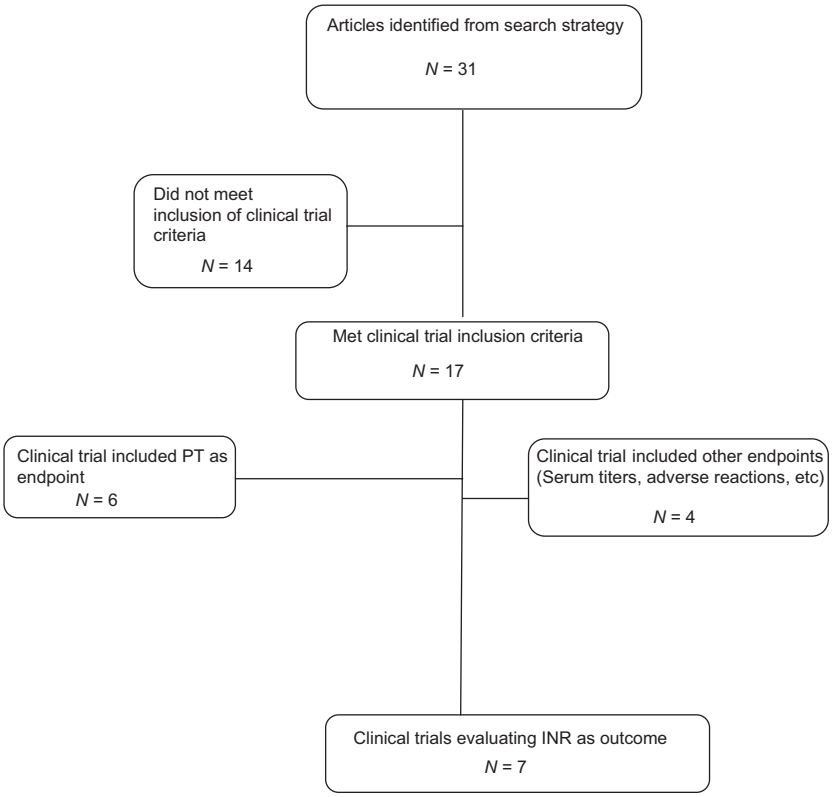

Fig. 1. Number and type of articles identified in the literature search and included or excluded in literature review.

Table 2. Summary of studies evaluating the effect of influenza vaccination on international normalized ratio (INR) during chronic warfarin therapy

Study design	Study pts., *N* (mean age, yrs)	Vaccine year, route of administration	Follow-up period post-vaccination	Statistically significant change in INR post-vaccination	Adverse bleeding events post-vaccination, (*N*)
PR[16]	106 (median >70)	2004/2005, NR	10 days	No	None
PCC[17]	90 (74)	2001/2002 (multiple brands used), IM	7–10 days	Yes	Epistaxis (1), muscular hematoma (1). Both events occurred only in patients with ≥0·5 change in INR
PCC[18]	73 (67 ± 10·9)	1998/1999, SQ	3 months	No	None
RC[19]	4923 (NR)	1992–2003, NR	28 days	No	NR
RCT, crossover[20]	100 (71·3 ± 9·2)	2004/2005, IM	28 days	No	Vaccine periods:[a] posttraumatic elbow hematoma (1), gingival bleeding (1), epistaxis (3), conjunctival hemorrhage (1) Placebo periods:[a] epistaxis (4), bruising (1)
RCT[21]	50 (60 ± 9)	NR SQ	21 days	No	NR during trial; None of the patients in the control group, who received the influenza vaccine after study conclusion, developed an adverse bleeding complication
PR[22]	9 (67·5 ± 14·5)	1988/1989 NR	30 days	No	Epistaxis (1) days 28–30; patient INR was lower during bleeding episode than baseline

PR, prospective review; PCC, prospective case–controlled; RC, retrospective cohort; RCT, randomized, controlled trial; NR, not reported; IM, intramuscular; SQ, subcutaneous.
[a]More events occurred in the vaccine-to-placebo crossover group

$P < 0{\cdot}00005$). In a subgroup analysis, 49 of 90 patients experienced a ≥0·5 change in mean INR (2·64 ± 0·95 before vs. 3·85 ± 0·98 after, $P < 0{\cdot}00001$), and two reports of epistaxis and muscular hematoma were reported within this subgroup. The remaining patients did not experience any INR changes, and no other adverse bleeding events were reported.

Poli *et al.*[18] evaluated patients considered stable on warfarin therapy for at least 6 months prior to study enrollment. All 73 patients in the study group who completed the trial received a single SQ influenza vaccination. Patient INRs in both the study and comparator group were evaluated during the 3 months before and after vaccination. Mean INRs were not reported, but no differences were found prior to or following vaccination within either group. In a subgroup analysis of patients older than 70 years of age, time spent below the therapeutic INR range appeared to be significantly longer in the study group following immunization (10% before immunization vs. 27% after, $P = 0{\cdot}001$). A similar observation was not noted in the comparator group during the same time period. None of the patients experienced an adverse bleeding event during the course of the study.

Prospective studies – placebo controlled

Farrow *et al.*[21] completed a single-blind study evaluating the effects of influenza and pneumococcal vaccines in 69 patients with a stable INR for at least 3 months prior to study entry while on warfarin. Twenty-five patients each were randomized to receive either an influenza vaccine or a saline control injection; the remaining patients received a pneumococcal vaccine. INR levels were taken immediately prior to vaccination and 2, 7 and 21 days post-vaccination. There were no statistically significant differences between groups in mean INR values at any time point post-vaccination. Two patients, one in the influenza vaccination group and one in the control group, required a dose reduction after INR levels rose to 4·5 on day 7 and 5·0 on day 21, respectively. Four patients in the influenza vaccine group vs. one patient in the control group required small increases in warfarin dosage to maintain an INR >2·0. No adverse events were reported in the patients receiving influenza vaccination.

A double-blind crossover study by Iorio *et al.*[20] assessed 100 patients receiving warfarin for >6 months and had a minimum of three consecutive therapeutic INRs that were documented at least 3 weeks apart. The study spanned 70 days and consisted of two 28-day study periods separated by a 14-day washout period. Fifty study subjects received an influenza vaccine during the first study period and a placebo injection during the second period, while the remaining study subjects received the injections in the reverse sequence. INR levels were assessed weekly during each study period. Following study completion, differences between mean INR, mean weekly doses of warfarin, and percentage of time spent outside the therapeutic range after treatment or placebo were not statistically significant. Likewise, data analysis using a linear mixed-effects model confirmed that vaccination did not significantly affect INR (regression coefficient −0·095, 95% CI −0·253 to 0·064; $P = 0{\cdot}24$) or weekly warfarin dose (regression coefficient 0·228, 95% CI −0·902 to 1·357; $P = 0{\cdot}69$). For adverse bleeding events, six events were reported during vaccination periods as compared to five events during placebo periods. More events were reported overall in the group that received the vaccine during the first study period (nine events in the vaccine to placebo group vs. two events in the placebo to vaccine group). The most common event reported was epistaxis; all events noted were considered minor and occurred within subtherapeutic to therapeutic INR ranges (1·5–3·3) with the exception of one bruising event that occurred at an INR of 6·9.

With the exception of the results of subgroup analyses and the study by Paliani *et al.*,[17] significant changes in INR were not observed post-vaccination.[16–22] In addition to INR, adverse bleeding events were also assessed in this review. No adverse bleeding episodes occurred in three of the seven studies.[16,18,21] The remaining reported events were considered minor in nature and not always associated with increases in INR.[17,22] Interestingly, in the study conducted by Iorio *et al.*,[20] most of the bleeding events occurred in patients who received the vaccine prior to placebo. In evaluating the nature of the bleeding events reported overall, this trend may be attributed to variability in anticoagulation response between and within patients rather than to the vaccine itself.

The studies reviewed included only patients stable on their current warfarin therapy, and this may not reflect clinical practice. Both interpatient and intrapatient variability in warfarin response should be considered when interpreting these studies. Three of the studies reviewed attempted to control for this potential confounder,[16,19,20] which may explain Kramer's index case and the inconsistent results seen in the studies reviewed. It remains questionable as to whether the reported studies had adequate statistical power. Iorio *et al.*[20] noted that a *post hoc* analysis demonstrated that the study was sufficiently powered. Such *post hoc* analyses may lead to flawed conclusions.

Notably, two of the studies reviewed documented a significant difference in INR changes post-vaccination despite relatively small sample sizes.[17,18] Paliani *et al.*[17] reported that mean INR values were significantly potentiated post-vaccination in the study group. However, this comparison was made between the study group and the comparator group. It is not known whether the increase in INR observed in the study group was statistically significant when compared with the mean baseline INR of the same set of patients. Making this comparison would have been beneficial to account for potential intrapatient variability in anticoagulation response over time as addressed by the studies conducted by MacCallum *et al.*[16] and Jackson *et al.*[19]

Through *post hoc* analysis, Poli *et al.*[18] detected a significant difference in time spent below the therapeutic range in a subgroup of elderly patients >70 years of age. As mean INR values were not reported, it may be possible that these patients had baseline INR values that were already on the threshold between therapeutic and subtherapeutic classifications. On another note, while *post hoc* subgroup analyses may provide further insight into the study data, such analyses are not considered to be ideal because there is an increased possibility of misinterpreting the data and detecting a significant difference when one may not exist.[23] Thus, conclusions made from observations noted in the subgroups mentioned by both Paliani *et al.*[17] and Poli *et al.*[18] should be made with caution.

Lastly, heterogeneity in methodology existed between the different studies in regard to the route of influenza vaccine administration and time of follow-up. Both of these factors could be considered as limitations in assessing the effect of influenza vaccine on INR levels. However, after further evaluation, neither of these factors are expected to have significantly impacted the results reported. For route of administration, subcutaneous injections were utilized in two studies in which significant differences were documented either overall or within a subgroup.[17,18] While IM injection is the recommended route for the influenza vaccine, there is some belief that patients on chronic anticoagulation should receive the immunization

subcutaneously to decrease the risk of muscular hematoma.[24] However, studies have shown that patients on anticoagulation therapy may receive the vaccine via the IM route without an increased risk of hematoma because the immunological response following either an IM or SQ injection is similar.[11,25] Therefore, the route of administration is not expected to be a confounder in assessing the effect of influenza vaccine on INR. Likewise, time after follow-up did not appear to affect whether a difference was observed in INR levels following immunization. In the index case study published by Kramer *et al.*,[5] an adverse bleeding effect was seen within 10 days of influenza vaccination. As described previously, Paliani *et al.*[17] noted a significant difference in INRs post-vaccination compared with the control group within the same time period. However, in the remaining six studies, INR levels were not significantly different up to 3 months after immunization.[16,18–22] This time frame is beyond that in which INR changes are expected.

WHAT IS NEW AND CONCLUSION

Overall, our review does not indicate a consistent, clinically relevant effect of influenza vaccines on INR of patients on chronic warfarin therapy. Isolated reports of variations in INR following influenza vaccination are likely attributed to other factors.

CONFLICT OF INTEREST

Authors of this manuscript have no reportable conflicts of interest.

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