Diagnosis, prevention and treatment of acute respiratory infections

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Chapter 6

Coagulation and inflammatory response after intramuscular or intradermal mRNA-1273 SARS-CoV-2 vaccine – secondary analysis of a randomized trial

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Abstract

Introduction
Fractional dosed intradermal vaccination produces antibody concentrations above the proposed proxy for protection against severe disease as compared with intramuscular vaccination and may be associated with a decreased prothrombotic effect.

Objectives
To assess changes in coagulation following standard dosed intramuscular or fractional dosed intradermal (1/5th of intramuscular) mRNA-1273 SARS-CoV-2 vaccine and to determine the association between the inflammatory response and coagulation.

Methods
This study was embedded in a randomized-controlled trial assessing the immunogenicity of an intradermal fractional dosed mRNA-1273 vaccine. Healthy participants, aged 18-30 years, were randomized (2:1) to receive either two doses of intradermal or intramuscular vaccine. Blood was drawn prior to first and second vaccination dose, one and two weeks after the second dose. The outcomes were changes in coagulation parameters (primary endpoint peak height of the thrombin generation curve) and inflammation (high sensitive- CRP).

Results
123 Participants were included (81 intradermal; 42 intramuscular). Peak height increased after vaccination (intramuscular 28.8 nmol; 95%CI: 6.3- 63.8; intradermal 17.3 nmol; 95%CI:12.5- 47.2) and recovered back to baseline within two weeks. Intramuscular vaccination showed a higher inflammatory response compared with intradermal vaccination (extra increase hs-CRP: 0.92 mg/L; 95%CI 0.2-1.7). Change in Endogenous Thrombin Potential was associated with change in hs-CRP (Beta 28.0; 95%CI 7.6- 48.3).

Conclusions
A transient increase in coagulability after mRNA-1273 SARS-CoV-2 vaccination occurred, which was associated with the inflammatory response. While intradermal administration showed antibody concentrations above the proposed proxy for protection against severe disease, it was associated with less systemic inflammation. Hence, intradermal vaccination may be safer.

Introduction

Vaccination against COVID-19 has played a pivotal role in containment of the COVID-19 pandemic.[1] Soon after the implementation of large scale SARS-CoV-2 vaccination, thrombotic events were reported as possible side-effects.[2] First reports described a pattern of thrombosis after vaccination with the vector based ChAdOx1 nCoV-19 vaccine, associated with platelet factor four (PF4) autoantibodies, a low platelet count, increased D67 dimer and decreased fibrinogen levels and was named vaccine induced thrombotic thrombocytopenia (VITT).[3,4] In addition, increased rates of venous thrombotic events (VTE) without thrombocytopenia were reported in the weeks after vector based (ChAdOx1nCoV-19 or Ad26.COV2.S) and (to a lesser extent) mRNA based vaccines (BNT162b2 or mRNA-1273).[5-9] This resulted in several changes in vaccination campaigns over the world.[10]

Several studies examining the effect of SARS-CoV-2 vaccination on coagulation parameters, such as the international normalized ratio (INR) and the activated partial thromboplastin time (APTT), showed contradictory results.[11-20] These parameters summarize only part of the coagulation system or are only relevant in patients receiving anticoagulant therapy, and may not accurately reflect alterations in the coagulation cascade. The thrombin generation assay (TGA) provides a global overview of both procoagulant and anticoagulant pathways.[21,22]

Intradermal (ID) vaccination is a dose-sparing strategy, providing immune responses equivalent to intramuscular (IM) vaccination, while using smaller vaccine doses and with the benefits of fewer systemic side effects.[23,24] A dose-sparing technique may particularly of interest to low- and middle- income countries.[25,26] Intradermal administrations with fractional dose has been proven successful in the past for several vaccines, such as influenza, rabies or hepatitis B vaccines.[27] During the COVID-19 pandemic, we conducted a randomized-controlled trial, comparing the immunogenicity of two 1/5th fractional ID doses and two full dose IM delivery of the mRNA-1273 (Moderna) vaccine, each 28 days apart, as a primary vaccination series.[28] Fractional dosing through ID vaccination showed antibody concentrations above the proposed proxy for protection against severe disease.[29]

It is possible that a fractional dose confers a lower thrombotic risk than a full dose vaccination. The aim of the present study was to assess the changes proxies for a prothrombotic change, i.e., levels of coagulation factor VIII, fibrinogen, and D-dimer levels, and thrombin generation parameters following mRNA-1273 vaccination, by dose, as well as the association between these changes and the inflammatory response.

Methods

Trial design

This study was a secondary analysis of an open-label, randomized-controlled trial at the Leiden University Medical Center in the Netherlands. The trial was approved by the Medical Ethical Committee Leiden, Den Haag, Delft (NL 76702.058.21) and registered in the International Clinical Trials Registry Platform (EUCTR2021-000454-26-NL). All

participants provided written informed consent.

Procedures

Eligible participants were adults, aged 18-30 years and predominantly White or of European ancestry. Participants with a past or intercurrent SARS-CoV-2 infection, determined by a positive SARS-CoV-2 PCR or seropositivity (positivity SARS-CoV-2 anti-N), were excluded. Other main exclusion criteria were prior SARS-CoV-2 vaccination, use of anticoagulants or steroids, hematological disease, or pregnancy.

Participants were randomized into three groups. The control group received two standard doses of 100 µg 28 days apart in the deltoid muscle (standard administration technique). Two experimental groups received two fractional doses (1/5th of the standard dose of 100 µg mRNA-1273) 28 days apart in the dermis of the deltoid region, one with the classical Mantoux technique and the other with a small needle (Bella-mu) designed for ID administration. Since both experimental groups showed similar immunogenicity results, they were combined in further analyses.[29] The randomization was done using sealed envelopes. The participant and site staff were unblinded, as the administration route differs.[29]

Blood was collected at day 1 (D1; before first dose), 29 (D29, before second dose), 36 (D36; one week after second dose) and 43 (D43). Fibrinogen, factor VIII, and D-dimer levels (reported in ng/ml D-dimer units) were measured to assess changes in coagulation, using a coagulometric clot detection method on an ACL TOP 700 analyzer (Werfen, Barcelona, Spain) as previously described using designated reagent (D-dimer HS 500, HemosIL, Werfen, MN, USA).[30] Thrombin generation (lag time, endogenous thrombin potential (ETP), peak height, time to peak, velocity index and time until the start of the tail of the curve) was measured using the Calibrated Automated Thrombogram® (Diagnostica Stago, Asinères, France) as previously described.[31] In the thrombin generation assay (TGA), coagulation is activated in plasma samples according to manufacturer's instructions, using a low amount of tissue factor and phospholipids followed by continuous measurement of thrombin formation and degradation. The ETP, which is the net result of pro- and anticoagulant potentials, is described by the height of the peak and the area under the curve. A higher peak height, ETP, start tail time or velocity index indicate hypercoagulability, while shorter lag time and time to peak represent hypercoagulability. The primary outcome of the TGA, measured in this study, was the peak height, as this is the most strongly associated with venous thrombosis risk.[32,33]

Inflammation was assessed by high sensitive (hs)-CRP from serum using the immunoassay analyzer COBAS CORE (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Outliers for coagulation and inflammation parameters (defined as 5 times the standard deviation (SD)) were excluded. At baseline we collected self-reported data on age, sex, medication use, body mass index (BMI) and comorbidities.

The change in coagulation parameters and inflammatory response was expressed as the difference between D1 and D36 (one week after the second vaccination), as these are relatively 'fast' processes and we expected that alterations in coagulation and inflammation normalize quickly. Participants with missing data on D1

or D36 were excluded from the analyses. To assess whether changes in coagulation or inflammation persist for a prolonged period, we determined the levels of the affected parameters again at D43. All changes relative to baseline were analyzed by univariate linear regression analyses. In addition, we compared change in distribution, i.e., the SDs of the parameters before and after vaccination, of all parameters. To assess whether there were differences between changes in coagulation or inflammation parameters after vaccination, stratified for type of vaccine administration (ID or IM), we adjusted for baseline values by using the difference between the post value (D36) and baseline value (D1) as the dependent variable and both the assigned type of administration (IM or ID) and baseline value (D1) as the independent variables in a linear regression analysis.

The association between the inflammatory response and change in coagulation was assessed for ID and IM vaccination combined and visualized by scatter plots and tested using univariate linear regression analysis.

Statistical analyses were done using STATA 16.1 for Windows (StataCorp, College Station, USA). Sample size was calculated based on the original trial.

Results

Between 14 June and 8 July 2021, 150 participants were enrolled, of whom 15 were excluded due to SARS-CoV-2 seropositivity at baseline or because of intercurrent SARS-CoV-2 infection before D29. Eleven additional participants were excluded because of missing coagulation data at baseline or D36 and one participant was excluded because of self-reported homozygosity for the Factor V Leiden mutation. Therefore, a total of 123 (82%) participants were included in the analyses of coagulation. Demographic characteristics of these participants are shown in table 1, stratified by group (ID vs IM). No major differences were observed between the ID and IM group, except a higher proportion of oral contraceptive use in the ID group than the IM group (26% vs 14%). For the analysis involving inflammatory markers, ten participants were excluded because of missing inflammation data at baseline or D36 and one participant was excluded because of a hs-CRP over 5 SD from the mean. The remaining 112 participants (75%) were included in the analysis on the association between coagulation and inflammation.

Differences between pre- and post-vaccination (D36-D1) for the coagulation and inflammation parameters are listed in table 2 and figure 1. The peak height increased in both the IM and ID groups (change in ID group: 17.3 nmol (95% Confidence Interval (CI): -12.5- 47.2); change in IM group: 28.8 nmol (95%CI: -6.3- 63.8). The SDs were larger at D36 than at D1 and differed between the measurements and the two groups (Peak height SD in IM group: before vaccination (D1) 69.2; after vaccination (D36) 90.9 and peak height SD in ID group: before vaccination (D1) 93.1; after vaccination (D36) 99.1), indicating that the magnitude of the change in peak height is variable between study participants.

Changes between D1 and D36 were observed for other parameters of thrombin potential, fibrinogen and D-dimer but not for FVIII levels (see supplemental figure 1). Most parameters were back to baseline levels at D43 (Peak height at D1:

Table 1. Characteristics of participants

	Intradermal	Intramuscular
N	81	42
Age, mean (SD)	22.1 (3.2)	23.5 (3.7)
Sex (female)	34 (42%)	17 (40%)
BMI, mean (SD)	24.4 (4.7)	23.4 (3.7)
Comorbidity	38 (47%)	17 (40%)
Psychiatric	16 (20%)	8 (19%)
Pulmonal	2 (2%)	0 (0%)
Allergy	16 (20%)	5 (12%)
Neurological	5 (6%)	1 (2%)
Other	11 (14%)	5 (12%)
Medication use	27 (33%)	13 (31%)
Antihistamine	9 (11%)	4 (10%)
Methamphetamine	8 (10%)	3 (7%)
Oral contraceptives	21 (26%)	6 (14%)
Other	8 (10%)	5 (12%)

BMI: Body Mass index. SD: Standard Deviation

219.4 nmol; at D36: 236.7 nmol; at D43: 223.6 nmol). Additionally, to confirm the quick normalization of coagulation after vaccination, we also compared coagulation parameters of D29 (just before second dose) to those of D1 and D43, to confirm if they were similar (see table 2 and supplementals). Hs-CRP increased in IM vaccinated participants (D36 relative to D1) but remained stable after ID vaccination (change in ID group: -0.1 mg/L (95% CI: -0.8 to 0.6) and change in IM group: 1.1 mg/L (95% CI: 0.1 to 2.1; see table 2 and figure 1).

After adjustment for baseline values, IM administration was associated with mild increase in all coagulation parameters and with an increase in hs-CRP compared with ID administration (extra increase peak height: 8.4 nmol; 95% CI -16.9 to 33.7; and extra increase hs-CRP: 0.92 mg/L; 95% CI 0.2 to 1.7; see table 3). Excluding participants using oral contraceptives did not alter these results (see supplemental table 3 and 4).

Association between coagulation and inflammation

The association between changes (e.g., delta) of coagulation parameters and change in hs-CRP between D1 and D36 are shown in table 4 and figure 2. A positive association was found between delta lag time (beta 0.13; 95%CI: 0.06 to 0.2), delta ETP (beta 28.0; 95%CI: 7.6 to 48.3), delta time to peak (beta 0.13; 95%CI: 0.01 to 0.27), delta time to tail (beta 0.26; 95%CI 0.00 to 0.51), delta fibrinogen (beta 14.6; 95%CI: 11.4 to 17.7), and delta Factor VIII (beta 2.2; 95%CI: 0.8 to 3.6) with delta hs-CRP. No association was found between the changes in the other coagulation parameters and the change in hs-CRP. Excluding participants with a delta hs-CRP under -5 or above 5 did not alter these results (results in supplemental figure 2).

Table 2. Coagulation and inflammation at baseline, before 2nd vaccine; one and two weeks after 2nd vaccine

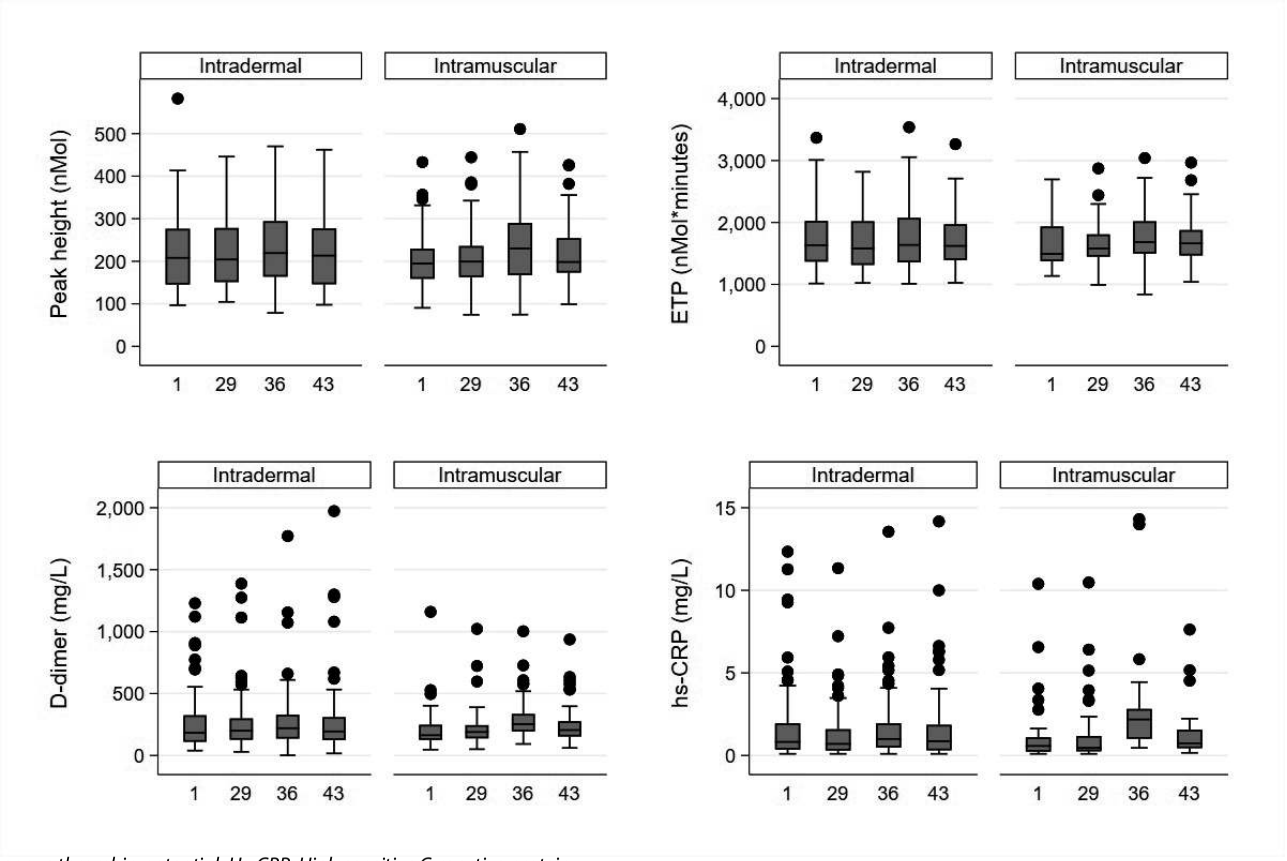
	Day 1 Baseline	Day 29 Before 2nd vaccine	Day 36 7 days after 2nd vaccine	Day 43 14 days after 2nd vaccine	Change between baseline and Day 36 (95% CI)
Intradermal, mean (SD)					
N	81	80	81	81	
Peak height (nmol)	219.4 (93.1)	223.9 (87.5)	236.7 (99.1)	223.6 (94.2)	17.3 (-12.5, 47.2)
Lag time (minutes)	5.8 (1.0)	5.9 (1.0)	5.6 (0.9)	5.7 (0.9)	-0.3 (-0.6, 0.03)
ETP (nmol x minutes)	1719.2 (467.4)	1687.5 (433.5)	1760.0 (515.1)	1690.9 (439.5)	40.7 (-111.9, 193.4)
Time to peak (minutes)	10.5 (1.7)	10.4 (1.8)	9.9 (1.7)	10.3 (1.9)	-0.6 (-1.1, -0.03)
Start tail time (minutes)	27.6 (3.2)	27.0 (3.0)	26.9 (3.4)	27.1 (3.0)	-0.8 (-1.8, 0.3)
Velocity index (nmol/minute)	52.2 (32.1)	56.5 (35.1)	63.9 (41.6)	58.5 (40.9)	11.7 (0.11, 23.3)
Fibrinogen (mg/dL)	273.4 (57.9)	272.5 (60.3)	284.3 (64.8)	277.9 (71.5)	10.9 (-8.2, 30.0)
Factor VIII (%)	100.1 (23.4)	101.5 (25.9)	99.6 (26.4)	100.8 (34.0)	-0.5 (-8.2, 7.3)
D-dimer (ng/ml)	258.6 (236.6)	266.7 (242.4)	274.7 (253.2)	279.9 (300.1)	16.1 (-60, 92.1)
Hs-CRP (ng/mL)	1.7 (2.5)	1.4 (1.8)	1.6 (2.0)	1.7 (2.4)	-0.1 (-0.8, 0.6)
Intramuscular, mean (SD)					
N	42	42	42	42	
Peak height (nmol)	202.9 (69.2)	210.0 (76.6)	231.7 (90.9)	222.0 (77.4)	28.8 (-6.3, 63.8)
Lag time (minutes)	5.8 (1.0)	5.9 (1.0)	6.0 (1.1)	5.8 (1.0)	0.1 (-0.3 , 0.6)
ETP (nmol x minutes)	1648.7 (386.0)	1666.7 (369.9)	1761.7 (433.7)	1748.2 (413.0)	113 (-65.2 , 291.2)
Time to peak (minutes)	10.8 (2.0)	10.8 (2.1)	10.4 (1.8)	10.4 (1.6)	-0.3 (-1.2 , 0.5)

Table 2. Coagulation and inflammation at baseline, before 2nd vaccine; one and two weeks after 2nd vaccine

	Day 1 Baseline	Day 29 Before 2nd vaccine	Day 36 7 days after 2nd vaccine	Day 43 14 days after 2nd vaccine	Change between baseline and Day 36 (95% CI)
Start tail time (minutes)	27.7 (3.0)	27.6 (3.1)	27.4 (2.8)	27.2 (2.7)	-0.2 (-1.6 , 1.1)
Velocity index (nmol/minute)	46.8 (28.9)	51.2 (33.0)	59.8 (39.1)	53.8 (31.5)	13.0 (-1.9 , 27.9)
Fibrinogen (mg/dL)	263.8 (57.4)	269.1 (58.7)	295.9 (59.0)	263.1 (43.7)	32.1 (6.8 , 57.4)
Factor VIII (%)	106.5 (24.1)	107.7 (25.4)	105.3 (25.9)	97.6 (26.9)	-1.1 (-12.0 , 9.7)
D-dimer (ng/ml)	215.8 (187.3)	233.2 (180.0)	299.2 (188.8)	261.6 (180.4)	83.5 (0.8 , 166.1)
Hs-CRP (ng/mL)	1.2 (2.0)	1.1 (1.5)	2.3 (2.3)	1.1 (1.1)	1.1 (0.1 , 2.1)

ETP: endogenous thrombin potential; Hs-CRP: High sensitive C-reactive protein; SD: standard deviation

Figure 1. Distribution of peak height, ETP, D-dimer and hs-CRP at each timepoint (1: baseline, 29: before 2nd dose, 36: one week after 2nd dose, 43: two weeks after 2nd dose), stratified for administration technique



ETP: endogenous thrombin potential; Hs-CRP: High sensitive C-reactive protein

Table 3. Difference in change after vaccination (D1 vs D36) between intramuscular and intradermal vaccination; adjusted for baseline

	Extra increase IM vs ID (95% CI) Adjusted for difference in baseline
Peak height (nmol)	8.4 (-16.9, 33.7)
Lag time (minutes)	0.35 (0.04, 0.7)
ETP (nmol x minutes)	66.7 (-36.0, 169.5)
Time to peak (minutes)	0.35 (-0.2, 0.9)
Start tail time (minutes)	0.54 (-0.6, 1.7)
Velocity index (nmol/minute)	1.76 (-9.5, 13.0)
Fibrinogen (mg/dL)	17.8 (-1.4, 36.9)
Factor VIII (%)	0.46 (-6.2, 7.1)
D-dimer (ng/ml)	49.9 (-24.1, 124.0)
Hs-CRP (ng/mL)	0.93 (0.2, 1.7

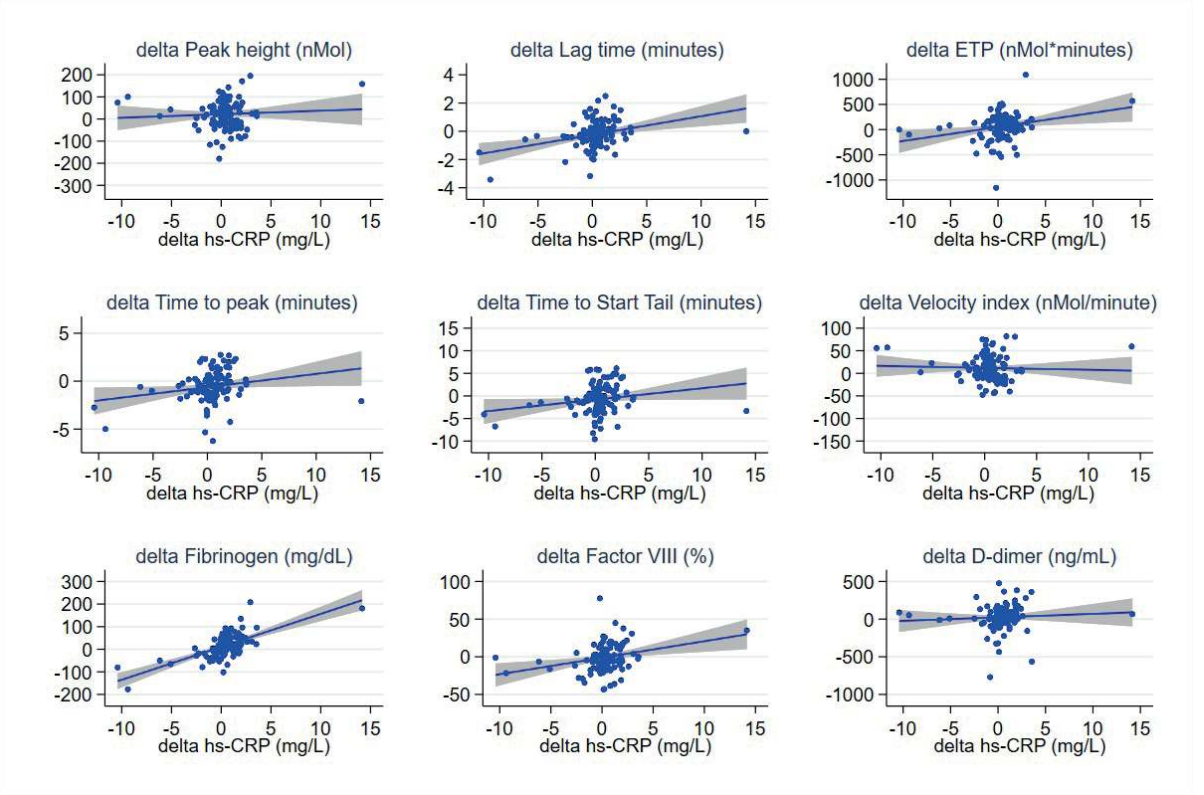
ETP: Endogenous Thrombin Potential; Hs-CRP: High sensitive C-reactive protein; IM; intramuscular; ID: intradermal; CI: confidence interval

Table 4. The association between the change of coagulation parameter and the change in the inflammatory response (delta hs-CRP) in all participants

	Units increase in the change in coagulation factors associated with one mmol increase in the change of hs-CRP (95% CI)
Peak height (nmol)	1.6 (-3.5, 6.6)
Lag time (minutes)	0.13 (0.06, 0.2)
ETP (nmol x minutes)	28.0 (7.6, 48.3)
Time to peak (minutes)	0.13 (0.01, 0.27)
Velocity index (nmol/minute)	-0.43 (-2.6, 1.7)
Start tail time (minutes)	0.26 (0.003, 0.51)
Fibrinogen (mg/dL)	14.6 (11.4, 17.7)
Factor VIII (%)	2.2 (0.8, 3.6)
D-dimer (ng/ml)	4.7 (-8.5, 17.8)

ETP: Endogenous Thrombin Potential; Hs-CRP: High sensitive C-reactive protein; CI: confidence interval

Figure 2. Scatter graphs for the association between the inflammatory response and changes after vaccination for each coagulation parameter; with fitted linear regression line



ETP: endogenous thrombin potential; Hs-CRP: High sensitive C-reactive protein

Discussion

SARS-CoV-2 vaccination with full dose IM or fractional dose (1/5th of standard dose) ID of the mRNA-1273 vaccine results in a transient prothrombotic state as evidenced by changes in peak height, endogenous thrombin potential, levels of fibrinogen and D-dimer. Particular the systemic inflammatory response was most pronounced in participants receiving the full dose of the vaccine intramuscularly as compared with the participants receiving the fractional dose intradermally. These changes in coagulation were associated with the inflammatory response.

Although no association was seen between the change in coagulation (D36-D1) and the inflammatory response after vaccination (D36-D1) in the primary coagulation endpoint (peak height), this was observed for multiple other coagulation endpoints, i.e., lag time, ETP, time to peak, the start tail time, fibrinogen and factor VIII. Particularly, the change in ETP was positively associated with the change in inflammation. This is most likely due to a longer time to complete inhibition of thrombin generation than a stronger and faster propagation of thrombin caused by inflammation (relative stronger association of start tail time with inflammation than lag time or time to peak or peak height). This suggests that inflammation causes the same amount of thrombin to be produced, however the inhibition of thrombin is slower. Fibrinogen and factor VIII are acute-phase proteins, which explains their association with inflammation. D-dimer was not associated with inflammation. This could be due to the relative shorter half-life of D-dimer (5 hours) as compared with CRP (19 hours), fibrinogen (40 hours) and factor VIII (12 hours), and therefore a possible change due to vaccination was not detectable anymore one week after vaccinations. It may seem contradictory that mean levels of FVIII do not change following vaccination (between D1 and D36), while there was an association between changes (e.g., delta) of FVIII and change in hs-CRP between D1 and D36. However, mean FVIII levels are measured on group level while the association between changes of FVIII and hs-CRP is assessed on an individual level.

Prior studies that evaluated coagulation parameters in SARS-CoV-2 vaccinated individuals using an unvaccinated control group also reported a change in the thrombohemorrhagic balance towards hypercoagulability.[16,18,19] Campello et al showed a transient increase in TGA at 3 days after vaccination, which normalized within 10 days.[14] Brambilla et al observed increased thrombin generation in 30 participants 8 days after receiving a mRNA vaccine.[13] Garabet et al. found no changes in thrombin generation or Ddimer in on average 11 days after vaccination, which might (similar to Campello et al.) be too long after vaccination to detect small and transient changes.[17] Despite an increased inflammatory response, Willems et al. found no changes in several activated coagulation factors in older participants in the 48 hours after vector-based vaccines.[20] However, all studies that reported an increase in coagulation parameters after vaccination concluded that these transient changes were not strong enough to be clinically relevant in an unselected population, and (similar to our study) no venous thrombotic events were observed.

The strengths of this study include the pre-post randomized design, preventing several possibilities of confounding. The only factor that could intervene in intra-individual change of coagulation may be an event of noticeable impact (e.g.,

infections, trauma). No such events were registered in the adverse event registration of the original randomized controlled trial and participants with a SARS-CoV-2 infection were excluded. In addition, the route of vaccine administration (ID or IM) was randomized. The only difference by chance between the two groups (oral contraceptive use) did not affect the conclusions.

Our study has limitations. The limited sample size did not allow a stratified analysis for low and high risk venous thrombosis groups. This is particularly evident in the analyses comparing ID with IM, in which confidence intervals were wide. In addition, the timepoints on which coagulation and inflammation was measured (7 days after second dose of vaccination) could be too late, especially for the inflammatory response. Potentially, the effects of vaccination on coagulation and inflammation are different in the week directly after vaccination, however our blood sample was drawn not earlier than 7 days after the vaccination. Furthermore, loss to follow-up was about 25%. However, this was evenly distributed between the ID and IM group, and unlikely to have been related to these laboratory analyses. Additionally, the cohort consisted of young individuals (<30 years of age), limiting generalizability to middle-aged and older individuals. However, (thrombotic) side effects of SARS-CoV-2 vaccinations are more often reported in young people and are of relative higher importance for young people, because of a lower risk of severe COVID-19 infection in the young.[34] The cohort was predominantly White or of European ancestry, therefore it is unsure if our result apply to other ethnicities. It is known that TG is affected by differences in blood collection, sample preparation and storage.[35] One might say that this lack of official standardization and reference values of TG results in limited external replicability of our results. However, all blood collections and analyzes were standardized and performed in a single lab, preventing biased measurements. In addition, by focusing on within individual changes, we expect that the lack of standardization of TG does not influence external replicability of our results. No measurement of coagulation and inflammation was performed in the first week after the first vaccine dose. Therefore, we do not know the effect of a single vaccination on coagulation and inflammation. However, most systemic side effects of the mRNA-1273 vaccine are reported especially after the second dose.[34] Von Willebrand Factor plays a key role in vascular inflammation and coagulation.[36] Unfortunately von Willebrand Factor was not measured in our study, which could have aided in the interpretation of our results. Because of the design of this study, we cannot conclude whether the smaller effect of ID vaccination than IM vaccination on coagulation and inflammation is caused by the administration technique, the fractional vaccine dose or both. Lastly, these results are only applicable for the mRNA-1273 vaccine. However, prior research suggests an even stronger effect on coagulation and inflammation after viral-vector based vaccines.[14,19,37]

Conclusion

We conclude that vaccination results in a transient prothrombotic state which is associated with the inflammatory response. ID vaccination with a 1/5th vaccine dose provokes a smaller systemic inflammatory response and might have a smaller effect on coagulation than IM vaccination, which indicates a benefit for ID administered or fractional dose (SARS-CoV-2) vaccines. Combined with other advantages of using

ID fractional dose vaccines, e.g., economic, ecologic and on public health domains, our results support the additional potential benefit of further implementation of ID administered vaccines. Furter research, using larger cohorts, should be performed on the identification of subgroups with higher risk of vaccine induced thrombosis. These groups could potentially benefit the most of ID administered vaccines.

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Competing interests
All authors declare no financial or non-financial competing interests.

Authorship Details
L. Visser and A. Roukens designed the original study. F. Rosendaal advised on the design of the study. W. van Dijk analyzed the data and wrote the manuscript. M. Prins and G. Roozen were responsible for the site work including recruitment, follow-up and data collection. L. Visser, A. Roukens, F. Rosendaal, M. Prins, G. Roozen, M. Roestenberg and A. van Hylckama Vlieg revised the manuscript.

Supplemental Material
All mentioned supplementary figures and tables in this chapter can be found by scanning this QR code.

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