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4 **Thromboelastography (TEG®) demonstrates that tinzaparin 4500 international units**

5 **has no detectable anticoagulant activity after caesarean section**

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Abstract

Background: Low molecular weight heparin is routinely used for thromboprophylaxis in pregnancy and the puerperium. Consensus guidelines recommend waiting 10-12 h after administration of a thromboprophylactic dose of low molecular weight heparin prior to performing a neuraxial block or removing an epidural catheter. Thromboelastography (TEG®) has been reported to be sensitive to the effects of enoxaparin at 4 h post-administration. The purpose of this study was to use TEG to study coagulation changes in the first 10 h after a thromboprophylactic dose of tinzaparin sodium and to try to ratify the current consensus guidelines with regards to the acceptable timing of neuraxial blockade and epidural catheter removal.

Methods: Twenty-four women were recruited post-caesarean section who were classified as low or intermediate risk of thrombosis. Blood samples were taken prior to the subcutaneous administration of 4500 international units of tinzaparin sodium, and at 4, 8 and 10 h post-dose. Standard TEG analyses were performed using plain and heparinase cuvettes and samples were also sent for laboratory anti-Xa assay. Thromboelastograph profiles were analysed to look for a low molecular weight heparin effect.

Results: Analysis revealed no significant differences in R time, K time, alpha angle or maximum amplitude between plain and heparinase samples at any time point. Apart from a small statistically significant (P=0.033) decrease in maximum amplitude of 2.8% (95% CI 0.3-5.4) at 4 h, there were no significant changes in coagulation for any TEG parameter. Anti-Xa levels were virtually undetectable in all patients over the 10 h period (median: 0.00 units.mL^{-1}) (range: 0.00-0.13 units.mL^{-1}).

Conclusions: In this study, a thromboprophylactic dose of 4500 units of tinzaparin sodium had little detectable effect on coagulation as assessed by TEG or anti-Xa assay. These findings would support consensus guidelines which state that it is acceptable to perform neuraxial blockade or remove an epidural catheter at 10-12 h after a thromboprophylactic dose of tinzaparin. Rather than suggesting a lack of anticoagulant activity, our findings indicate that TEG may not have the sensitivity to detect a tinzaparin effect when this particular dose is used in this patient group. Further larger scale research is needed to elucidate the precise mechanism of action of different low molecular weight heparins in the pregnant population, and to further assess the ability of these drugs to reduce thrombosis risk.

Keywords*:* Thromboelastography; TEG; low molecular weight heparin; tinzaparin

Introduction

Thromboembolic disease is widely recognised as an important cause of maternal morbidity and mortality in the UK. Indeed, the 2009-2012 MBRRACE-UK report highlighted that thromboembolic disease was once again the leading direct cause of maternal death for that triennium, as it had been for all triennia analysed in confidential enquiries prior to 2006-2008.[1] Low molecular weight heparin (LMWH) is prescribed for thromboprophylaxis post-caesarean section and for high risk women in the puerperium. It is also being used with increasing frequency in the antenatal period for women identified as being at particularly high risk of thromboembolism during pregnancy itself.[2,3]

The use of LMWH in pregnancy may create a problem for anaesthetists with regards to the timing of insertion of neuraxial blocks and also for the removal of epidural catheters. The development of a vertebral canal haematoma is a small but potentially devastating risk of spinal or epidural insertion, with a reported incidence of 0.85 per 100,000 central neuraxial blocks.[4] This risk is increased further in the context of an anticoagulated patient. In order to reduce the risk of haematoma development, current UK and international consensus guidelines recommend that performance of a neuraxial block or removal of an epidural catheter should not be carried out until 10-12 h after a thromboprophylactic dose of LMWH.[5,6,7] These guidelines were devised for use in non-pregnant patients, but have been extrapolated for use in the pregnant population as well, even though these women are known to be hypercoagulable.

Thromboelastography (TEG®) is a point of care test of global coagulation state. It uses the viscoelastic properties of blood to assess the interaction between all of the components involved in clot formation and dissolution. Clinicians are becoming increasingly familiar with the use of TEG in major haemorrhage where it may be of help in guiding appropriate blood product replacement. Recent studies, however, have also demonstrated that TEG can detect the effect of LMWH.[8,9,10] This may be particularly useful since current standard coagulation tests do not detect a LMWH effect, and although anti-Xa assay can be performed, this is impractical for the rapid assessment of coagulation state.

The TEG reaction time (R time) is the time from the start of the sample until initial fibrin strand formation, and has been shown to be the most sensitive TEG parameter to the effects

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103 of LMWH.[8,11] It has previously been shown that heparinase neutralises not only the effects of

104 heparin, but also of LMWH, and therefore heparinase TEG samples may be used as a

105 control.[9] Using plain and heparinase samples, it has previously been reported that the R time

106 is sensitive to the effects of sub-cutaneous enoxaparin 40 mg at 4 h post administration in a

107 post-caesarean section population of women.[10]

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109 In accordance with current UK guidance,[2] our unit routinely uses tinzaparin sodium 4500

110 international units (i.u.) for thromboprophylaxis in pregnancy and the puerperium. The

111 purpose of this prospective observational study was to use TEG to try to ratify the current

112 consensus guidelines which recommend waiting 10-12 h after a thromboprophylactic dose of

113 LMWH, prior to performing a neuraxial block or removing an epidural catheter. We made

114 three hypotheses: firstly that TEG would act as a sensitive tool in detecting the effect of a

115 thromboprophylactic dose of tinzaparin; secondly that there would be a peak effect on R time

116 prolongation at 4 h post-tinzaparin administration; and finally that TEG would no longer

117 detect the presence of tinzaparin at 10 h post-dose.

118

119 **Methods**

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121 Approval for the study was obtained from the local ethical and institutional review board

122 (NRES Committee London - Hampstead REC reference: 11/LO/1084). After obtaining

123 written informed consent, ASA 1 and 2 women were enrolled who had undergone category 1-

124 3 caesarean section[12] under epidural or combined spinal-epidural anaesthesia. All women

125 recruited to the study were between 20 and 45 years of age, with a singleton term pregnancy,

126 and were classified as being at low or moderate risk of thromboembolism according to

127 national guidelines set out by the Royal College of Obstetricians and Gynaecologists.[2]

128

129 Women were excluded from taking part in the study if they were deemed to be in a high risk

130 category for thromboembolism according to these guidelines. Such exclusions encompassed

131 those women who had been taking anticoagulant medication or had required

132 thromboprophylaxis in the antenatal period, women with a body mass index (BMI) greater

133 than 35 kg m^{-2}, those with pre-eclampsia (as defined by local guidelines), and women who

134 had suffered a major postpartum haemorrhage ($\geq$1000 mL) and/or required a blood

135 transfusion intra-operatively or within the first 24 h post-delivery.

136

137 For each patient, a dedicated 16-gauge (16-G) cannula was inserted and used preferentially

138 for all blood sampling. The venous blood samples were taken post-caesarean section

139 immediately prior to the first subcutaneous administration of a standard thromboprophylactic

140 dose of 4500 i.u. of tinzaparin (Innohep®, LEO Pharmaceutical Products, Denmark),[13] and

141 again at 4, 8 and 10 h post-tinzaparin. For all patients, the tinzaparin was administered within

142 4 hours of delivery as an injection into the lateral thigh and in accordance with the

143 manufacturer's recommended injection technique. A 21-G needle and syringe were used for

144 venepuncture in a small number of cases where cannula aspiration was not possible, and

145 provided maternal consent was given for this alternative sampling technique.

146

147 The first 2 mL of blood drawn from the cannula was discarded each time; approximately 15

148 mL of blood was then sampled with l mL being used for TEG analysis as described below.

149 The remaining blood was divided between two tubes containing tri-sodium citrate (BD

150 Vacutainer® 9NC 0.109M), and one tube containing ethylene-diamine-tetra-acetic acid (BD

151 Vacutainer® K2 EDTA). The three tubes were sent immediately to the hospital haematology

152 laboratory where the EDTA sample was analysed for routine full blood count. One of the

153 citrated samples was used for determination of the Activated Partial Thromboplastin Time

154 (APTT) and the other for anti-Xa assay (Sysmex® CA 7000UK Ltd).

155

156 The 1 mL samples of blood used for TEG analysis were placed immediately into kaolin vials

157 (Haemoscope, Niles, IL, USA) which were inverted five times according to the

158 manufacturer's recommendations. At each time point in the study, two 360 µL kaolin-

159 activated samples were individually pipetted into pre-warmed (37 ℃) plain and heparinase

160 cuvette cups. The heparinase coated cuvettes were used as control samples to allow the

161 identification of a tinzaparin effect. A heparin effect was defined as a TEG R time >25%

162 longer than a heparinase corrected control.[14,15] The plain and heparinase samples were run in

163 parallel on a thromboelastograph (TEG) coagulation analyser (TEG® Haemostasis Analyser

164 5000, Haemoscope Corporation, Niles, IL, USA), which was calibrated daily. All samples

165 were analysed within 4 min of blood collection and the channels on the TEG analyser were

166 alternated between plain and heparinase samples at each time point to reduce bias.

167

168 Computerised thromboelastographs were obtained for each of the paired samples prior to

169 tinzaparin administration and at 4, 8 and 10 h post-dose. The following standard TEG

170 parameters were recorded for each patient at the different time points: R time, K time, alpha

171 (α) angle, maximum amplitude (MA) and coagulation index (CI). Other data collected in the

172 study included age, weight, height, parity, gestation, reason for caesarean section, intra-

173 operative blood loss and total volume of intravenous fluid received. Data are presented as

174 mean (SD), median [interquartiles] and count as appropriate.

175

176 **Statistical Analysis**

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178 Sample size estimates suggested the recruitment of 24 patients was necessary to detect a

179 nominal 20% (SD 25%) anticoagulant effect as significant. Calculations suggested that this

180 sample size would give the study 90% power to detect changes of 20% in R time for the

181 effect of LMWH, at a Bonferroni corrected threshold $P<0.0125$ for multiple comparisons to

182 keep the overall type I error rate at <5%. Data analyses included linear mixed modelling

183 (LMM), repeated measures analysis of variance (RMANOVA) and Bonferroni post-test

184 correction. Statistical significance was defined as $P<0.05$. Data were analysed using Number

185 Cruncher Statistical Systems (NCSS) version 9.0 software (NCSS Inc., Kaysville UT).

186

187 **Results**

188

189 Twenty-five women were enrolled in the study. Data from one patient were excluded since

190 the TEG parameters and laboratory values obtained were anomalous. Numerical data from

191 the remaining 24 patients were used for statistical analyses. The demographic, obstetric and

192 operative data for these women is shown in Table 1.

193

194 There was no statistically significant difference in the R time at any time point compared to

195 the baseline time (Figure 1). There was a small statistically significant reduction in the MA of

196 2.8% (95% CI 0.3-5.4) at 4 h ($P=0.033$) compared to the baseline, but this difference was not

197 identifiable at any other time point (Figure 2). Similarly, no significant differences were

198 detected in the α angle or K time at any point (Figure 3 and 4).

199

200 Figures 5-8 show the individual patient differences between plain and heparinase TEG

201 parameters. Tinzaparin effects are shown by negative values for R and K times and positive

202 values for α angle and MA. No statistically significant anticoagulant effect of tinzaparin was

203 demonstrated.

205 A heparin effect (defined as a TEG R time >25% longer than a heparinase corrected control R

206 time) was only identified in three women in the study (Table 2), and linear mixed modelling

207 showed no statistically significant difference in the R time between the plain and heparinase

208 samples at any time point.

210 Anti-Xa levels were virtually undetectable by anti-Xa assay (median: 0.00 units.mL^{-1}) (range:

211 0.00-0.13 units.mL^{-1}) (Table 3). Only 4 patients in the study (16.7%) (95% CI 4.7-37.4)

212 reached the thromboprophylactic level of 0.1 units.mL^{-1} at any time point, and this occurred

213 in only 1 of the 3 patients in whom a heparin effect was identified (Table 2). No patients

214 developed a neuraxial haematoma.

216 **Discussion**

218 This study found that, for practical purposes, a standard thromboprophylactic dose of

219 tinzaparin 4500 i.u. was not detectable by TEG at any time point up to 10 h after

220 administration in a post-caesarean section population of women. Although a tiny statistically

221 significant reduction in MA was observed at 4 h post-dose, this was too small to be

222 translatable into a clinically significant effect. Of further interest, the presence of tinzaparin

223 was also not detected in the majority of patients using anti-Xa assay, even though this is the

224 most commonly utilised laboratory test for the identification of LMWH.

226 All parturients who were enrolled in our study had a booking weight of between 50 and 90 kg

227 and were of normal BMI. The manufacturer recommends no dose adjustment of tinzaparin

228 during pregnancy and we used the recommended postpartum thromboprophylactic dose of

229 tinzaparin for women in this weight category.[2,10] Our findings do not necessarily mean that

230 this dose is clinically ineffective in reducing the risk of venous thromboembolism (VTE) in

231 this population. Several systematic reviews have demonstrated that this dose of tinzaparin is

232 associated with a very low incidence of both postpartum and antenatal VTE.[16,17] It is more

233 plausible that although we used the recommended thromboprophylactic dose of tinzaparin in

234 these women, that this dose was insufficient to produce a change in TEG parameters. Our

235 study findings do not affirm that tinzaparin has no anticoagulant activity and a significantly

236 larger sample size would be needed to assess anticoagulant effects in more detail.

238 The dose we used also resulted in virtually undetectable anti-Xa levels, again suggesting

239 significant underdosing. However this interpretation should be viewed with caution. Routine

240 monitoring of LMWH activity is not usually necessary in a clinical setting, since it results in

241 a reproducible anticoagulant response when dosed on a weight-adjusted basis.[18] Anti-Xa

242 assay is widely accepted as the laboratory technique of choice in cases where identification of

243 the antithrombotic effect of LMWH is still required, and we used this assay to try to detect

244 the presence of tinzaparin in our study. Previous studies, however, have remarked upon the

245 potential multifactorial mechanism of action of LMWH and on the considerable variation in

246 anti-Xa:IIa activity between different types of LMWH (Table 4).[18, 19] Tinzaparin has the

247 lowest ratio of Xa:IIa activity amongst the most routinely prescribed of the low molecular

248 weight heparins. Consequently, the utilisation of anti-Xa assay to identify the presence of this

249 particular agent may not have been the most suitable technique, and may help to explain the

250 almost negligible levels of anti-Xa activity we found in this study.

251

252 The inability of our study to detect an effect of tinzaparin on coagulation using TEG was

253 unexpected and is in contrast to previous work which has demonstrated the sensitivity of

254 TEG and anti-Xa levels to the effects of other types of LMWH. Using blood samples

255 collected from a healthy male population, Coppell et al demonstrated in vitro that TEG MA

256 was reduced in the presence of even very low concentrations (<0.1 U/mL) of dalteparin

257 ($P<0.0001$).[9] In a later study, similarly focussing on the use of dalteparin (single

258 subcutaneous dose of 120 i.u/kg), Artang et al also demonstrated in vivo in adult male

259 volunteers, that there was a strong correlation between all the basic TEG parameters and anti-

260 Xa levels after dosing with this particular LMWH. In this latter study, the TEG R time was

261 found to be the most sensitive of the TEG parameters to the presence of dalteparin.[8]

262

263 In a study conducted by Macafee et al, reference ranges were derived for both TEG and

264 standard coagulation tests in term parturients undergoing caesarean section under spinal

265 anaesthesia.[10] In this study, enoxaparin rather than tinzaparin was used as the standard post-

266 caesarean section thromboprophylactic agent. Venous blood samples were taken 4 h after

267 post-caesarean administration of enoxaparin, and TEG analysis was performed under very

268 similar experimental conditions to those described in our study. The group demonstrated that

269 TEG R time, MA and CI were sensitive to the effects of enoxaparin at 4 h post

270 administration, with TEG parameters suggesting that 73% of the women were less coagulable

271 at this time point when comparison was made with their pre-operative baseline samples. No

272 such effect was seen in our study with mean R times being shorter at 4 h compared to

273 baseline. A heparin effect has previously been defined as a TEG R time >25% longer than a

274 heparinase corrected control in studies looking at the effects on TEG of the administration of

275 unfractionated heparin.[14,15] Using LMWH, Macafee et al demonstrated in their study that

276 such an effect was present in 52% of parturients who underwent 4 h post-enoxaparin TEG

277 analysis. In our study, such a heparin effect was only demonstrated in three women who had

278 received tinzaparin. Since it has been shown that TEG can be used to detect the presence of

279 enoxaparin in a similar post-caesarean section population of women, it is likely that TEG

280 would be able to detect the presence of tinzaparin if given at a larger dose. These findings

281 suggest that 40 mg enoxaparin has a greater anticoagulant effect than tinzaparin 4500 i.u.

282

283 TEG has been used to direct management during labour for women receiving therapeutic

284 tinzaparin.[20] One of the reasons for carrying out our study was to explore the possibility that

285 information obtained from TEG could be used to guide safe insertion of neuraxial blockade

286 or epidural catheter removal in women receiving thromboprophylactic LMWH. In theory, by

287 using plain and heparinase samples together, any LMWH effect could be clearly

288 demonstrated. Conversely, when no difference is demonstrated, this would imply that the

289 LMWH effect has worn off. Unfortunately, in this study no differences were shown between

290 plain and heparinase samples when using tinzaparin at any time point. This raises concerns

291 that TEG may not be able to detect a tinzaparin effect, even though it has detected a LMWH

292 effect in other studies with different types of LMWH. However, the lack of effect of

293 tinzaparin at this dose at 10 h would lend support to the consensus view that it is acceptable

294 to perform neuraxial blockade or remove an epidural catheter at that time.

295

296 There are some limitations to our study. Our patients had undergone category 1-3 caesarean

297 section[12] with the disadvantage that the surgery itself may have had a prothrombotic effect. In

298 addition, some women had been in labour for a variable amount of time pre-caesarean

299 delivery, and some came straight to theatre without being allowed to labour at all. These

300 differences may have had a bearing on the coagulation profiles and subsequent results

301 obtained, and the findings may not therefore be more widely applicable to an antenatal

302 population. However antenatal women receiving LMWH themselves fall into a particularly

303 high risk category for thromboembolic disease and could also be regarded as a heterogeneous

304 pro-thrombotic population. Clinically, no distinction is made in terms of the LMWH protocol

305 used, with all women receiving the same dose, regardless of the indication for the

thromboprophylaxis. Consequently we felt it was acceptable to recruit women on the first morning after their caesarean section. This had the added advantage that all samples could be processed during daylight hours and avoided the inconvenience for patients of having blood samples taken during the night.

Most patients had venous blood samples drawn from a dedicated 16-G cannula for subsequent TEG and laboratory analysis. Women underwent venepuncture using a 21-G needle and syringe in cases where there were initial or subsequent difficulties in aspirating blood from the cannula, or on occasion due to maternal preference from the outset. Although all TEG samples were placed immediately into kaolin and analysed within 4 min of collection, the non-standardised method of venepuncture used in this study may have resulted in the premature activation of coagulation in some samples, and this may have affected the TEG results obtained. This difficulty in being able to consistently aspirate samples from a cannula, however, was also encountered by Macafee et al who were still able to demonstrate that TEG was sensitive to the effects of enoxaparin.[10]

In conclusion, a thromboprophylactic dose of tinzaparin 4500 i.u. post-caesarean section appeared to have little detectable effect on coagulation as assessed by TEG or anti-Xa levels. These findings would support current consensus guidelines which state that it is acceptable to perform a neuraxial block (or remove an epidural catheter) at 10–12 h after a thromboprophylactic dose in this patient population. The findings also raise the possibility that these actions may be considered earlier than 10 h, however a substantially larger study would be needed to examine whether women who had received neuraxial blockade followed by tinzaparin thromboprophylaxis were at risk of neuraxial haematoma. Contrary to a similar study using enoxaparin,[10] a tinzaparin effect was not detectable by TEG or anti-Xa levels in the majority of patients in this study. This does not mean that tinzaparin has no anticoagulant effect. It is more probable that these tests do not possess the sensitivity to detect this dose of tinzaparin in this particular population. Further larger scale research is needed to elucidate the precise mechanism of action of different low molecular weight heparins in the pregnant population, and to further assess the ability of these drugs to reduce thrombosis risk.

Disclosure

342 **Acknowledgements**

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