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EDITORIAL

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Paralysis analysis – does choice of muscle relaxant for obstetric general anaesthesia influence neonatal outcomes?

Several modifications to the well-known obstetric general anaesthetic technique, succinctly characterised by '*Thio, Sux, Tube*', have been proposed over recent years and include the use of rocuronium instead of suxamethonium for neuromuscular blockade.[1–3] However, the evidence base on which many such recommendations are made is weak. A literature search of scientific publications relating to obstetric general anaesthesia and airway management from 1950 to 2014 found that few quality studies exist. Consequently, the 2015 Obstetric Anaesthetists' Association and Difficult Airway Society obstetric-specific airway guidelines are based on expert consensus, rather than high-level evidence.[2] This comes as no surprise, because obstetric general anaesthesia is a challenging area to study. Furthermore, general anaesthesia may affect maternal *and* neonatal outcomes and both require consideration – an intervention may benefit one, but be of detriment to the other. In the anaesthetic literature at least, it would seem that more attention has been placed on the former than the latter, so it is uncommon for a randomised trial to come to light that investigated outcomes of over 500 neonates delivered by caesarean delivery under general anaesthesia. The study by Kosinova et al. published in this edition of the *International Journal of Obstetric Anesthesia*, randomised 488 women to suxamethonium 1 mg/kg or rocuronium 1 mg/kg, following propofol 2 mg/kg, for rapid sequence induction (RSI) of general anaesthesia for caesarean section. They found lower 1-min Apgar scores in neonates born to women who received rocuronium.[4] However, before drawing any hasty conclusions from this finding, readers are advised to consider the study carefully because, as is sometimes the case, things are not entirely as they might first seem.

Despite description of several modifications to the 'traditional' RSI technique,[5] tracheal intubation facilitated by neuromuscular blockade remains a cornerstone of obstetric general anaesthesia. The ideal muscle relaxant in this setting has been debated, but the two contenders most commonly found 'slugging it out' in the 'pro–con' arena are suxamethonium and rocuronium (assisted by its reversal agent sugammadex).[6,7]

Rocuronium, a steroidal non-depolarising neuromuscular blocking drug, was introduced into clinical practice in 1994 and obstetric use soon followed.[8] In this comprehensive clinical study, albeit of a small sample of 40 pregnant women, Abouleish et al. measured several outcomes including the onset of action, intubating conditions, maternal and neonatal side effects, and maternal blood and neonatal cord blood concentrations of rocuronium (to determine placental transfer). However, before the introduction of sugammadex, dosing rocuronium to achieve a suitably rapid onset of action for RSI, without the resultant neuromuscular block exceeding the time taken to perform the caesarean delivery, was challenging. Consequently, the ideal rocuronium dose in this setting has remained unclear and ranges from 0.6 to 1.2 mg/kg.[9]

The introduction of sugammadex has fundamentally changed the landscape of neuromuscular pharmacology. Sugammadex reversal of rocuronium (0.6 mg/kg)-induced neuromuscular block for obstetric RSI was first reported in 2010.[10] The authors of a subsequent study of rocuronium 1.2 mg/kg reversed with sugammadex 4 mg/kg at caesarean delivery concluded that lower doses of rocuronium could no longer be recommended in the obstetric population. However, this was a small, uncontrolled investigation with limited neonatal outcome data.[11] Bringing us right up to date is the work by Kosinova et al., published as studies in this journal[4] and another journal.[12] This group originally designed a study to primarily investigate maternal outcomes after general anaesthesia for caesarean delivery in 240 women, given rocuronium 1 mg/kg (reversed with sugammadex) or suxamethonium 1 mg/kg. They found no difference in time to intubation (the primary outcome), but less resistance to laryngoscopy and a lower incidence of myalgia in the rocuronium group. They concluded that rocuronium was non-inferior to suxamethonium for time to intubation; and may have other benefits for caesarean delivery.[12]

The study published in this edition of the journal, by the same group, continues the story by focussing on neonatal outcomes.[4] However, when the manuscript was received it was apparent that there were some methodological issues and it is important that these and other limitations of the study are acknowledged. In their original study, designed and powered to investigate a maternal outcome, the authors found that the incidence of low Apgar scores (<7) at 1- and 5-min

was greater in neonates born to women administered rocuronium, compared to suxamethonium. Given these were secondary outcome data, the authors correctly avoided speculating on the relevance of the finding and instead suggested a future study, to correlate cord blood concentrations of rocuronium with Apgar scores and neonatal neuromuscular function.[12] Rather than design and conduct such a study, the authors took the somewhat unusual step of extending their original study to enable recruitment of an 'adequate' sample to investigate this neonatal outcome. Thus, a further 248 women were recruited in an extension to the original study, and after including neonatal data from the original study of 240 women, 525 neonates, born to 488 women, randomised to receive rocuronium or suxamethonium, were studied and the results published here.[4]

Before considering their findings, the methodological issues deserve highlighting. First, no *a priori* power calculation for determining the sample size required to detect a difference in the neonatal outcome under investigation was performed and second, in extending a study ostensibly designed to investigate maternal outcomes, important data relating to neonatal condition and transplacental passage of muscle relaxant were not collected. These issues limit the robustness of the results. However, the authors considered the final number of subjects enrolled was adequate to determine a 10% difference in the incidence of low 1-min Apgar score. As the neonatologists were blinded to the study intervention in both phases of the study, the authors felt their results were reliable. In analysing the cumulative data from the 525 newborns, the secondary outcome finding of the original study remained – the use of rocuronium was associated with lower neonatal Apgar scores at 1-min compared with suxamethonium. Importantly, there were no differences in Apgar scores at 5- or 10-min; or in umbilical artery pH, pCO_2, pO_2 or lactate. Rocuronium concentration in either maternal blood or neonatal cord blood was not measured; and neonatal neuromuscular function was not assessed.

What are the possible explanations for this finding? Was this simply a consequence of a type 1 error, due to the study being underpowered? Perhaps, given the methodological issues highlighted above. Were neonates in the rocuronium group simply exposed to a longer period of general anaesthesia? Yes, but this time period did not reach significance. Was there a difference in the characteristics of the groups with respect to risk of poorer neonatal outcome in the rocuronium group? Apparently not and the same result was found when newborns with fetal pathology or signs of fetal hypoxia were excluded from analysis. Or can this finding be explained by neonatal curarisation, due to transplacental passage of rocuronium? Possibly, and more on that later. Importantly, if this a genuine finding, then what is the relevance of a transient reduction in neonatal Apgar score following maternal administration of rocuronium?

The Apgar score is considered an accepted method of reporting the status of the newborn immediately after birth and at subsequent time points; and the response to resuscitation, if required.[13] However, several factors influence the score, including gestational age, maternal sedation, and inter-observer variability in assessment of some more subjective components. Furthermore, the relevance of a low 1-min Apgar score is uncertain, especially in the context of a normal score at 5- and 10-min. Unfortunately, individual components of the Apgar score or requirement for supportive interventions (e.g. airway suctioning, respiratory support) were not recorded in Kosinova et al.'s study, so whether choice of maternal muscle relaxant influenced certain elements of the neonatal condition is unknown.

Data on placental transfer of rocuronium are limited, but it is worth considering what we do (and don't) know. Drug transfer across the placenta occurs via several mechanisms and is dependent on the pharmacological properties of the drug and physical characteristics of the placenta, including placental blood flow and maternal and fetal pH.[14] Comparison of drug concentrations in the maternal and neonatal cord blood at the time of delivery provide a surrogate indicator of the degree of drug transfer across the placenta. The ratio of umbilical vein (UV) to maternal vein (MV) (or in some studies, maternal artery) drug concentration is commonly presented to indicate the degree of placental transfer. While UV:MV ratios have been described for many drugs used in obstetric anaesthesia, variations between and within individuals are reported.[8,15] Furthermore, measurement of UV drug concentration does not always accurately represent fetal tissue exposure, because most of the UV blood in-utero flows to the fetal liver, where a drug may be exposed to first-pass metabolism before undergoing further dilution in the circulation. However, muscle relaxants undergo low placental transfer as a result of being highly ionized at physiological pH; and large, poorly lipid soluble molecules. The UV:MV ratio has been reported for most neuromuscular blocking drugs, but the value has been derived on the whole from small studies. Suxamethonium does not cross the placenta when administered in usual clinical doses.[16] The UV:MV ratio for rocuronium of 0.16 was determined from a study of 32 women and their newborns exposed to a dose of 0.6 mg/kg.[8] Rocuronium 1 mg/kg administered in Kosinova et al.'s study represents a dose more than three times the effective dose $(ED)_{95}$; and fetal plasma concentration of other muscle relaxants has been shown to increase with higher maternal dosing.[16,17] To my knowledge, there are no data on placental transfer of rocuronium after doses greater than 0.6 mg/kg. In the absence of maternal and neonatal blood rocuronium concentrations or assessment of neonatal neuromuscu-

lar function, one cannot conclude with confidence that the lower 1-min Apgar scores in Kosinova et al.'s study were due to partial curarisation following transplacental passage of rocuronium. However, this explanation is plausible and deserves further investigation.

As a journal reviewer and reader, there is a tendency to focus (appropriately but perhaps at times disproportionately) on the limitations of a study. While Kosinova et al.'s study has weaknesses, its strengths must be recognised. These data are unique and obtained from one of the largest randomised trials of a specific intervention in obstetric general anaesthesia. In view of the problematic study design and uncertainties regarding the authors' findings, the results are not sufficiently robust for strong conclusions or recommendations to be made. Misinterpretation may have clinical implications, so taking a circumspect position is prudent. If maternal rocuronium 1 mg/kg adversely affects neonatal outcome, this would appear to be short-lived and the relevance limited, given the neonatal support commonly available at caesarean delivery under general anaesthesia. It is with some reluctance to end with the oft-used conclusion that "further research is required", but in this instance, it seems most fitting. The work by Kosinova et al. makes an important contribution to the literature. It serves to remind us that obstetric general anaesthesia may impact both mother and child, and of our duty to strive to optimise the outcomes of both.

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