Editorial

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There is (probably) no (meaningful) difference in (most) outcomes between 'spinal' and 'general' anaesthesia for hip fracture surgery … so let's move forward in research and practice.

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In a recent issue of the *British Journal of Anaesthesia*, Kunutsor and colleagues report a systematic review and meta-analysis of randomised controlled trials (RCTs) concerning mode of anaesthesia for hip fracture surgery, published since 2003.[1] They make comparisons for a series of outcomes drawn from a consensus-based core outcome set and patient and public involvement (PPI) in 3866 patients who underwent either spinal (SA, n=1874) or general (GA, n=1992) anaesthesia.[1,2] With the exception of acute kidney injury (two studies, RR=0.59 (CI=0.39-0.89), favours SA), no *statistically* significant differences were found for 10 core outcomes,[2] including delirium (nine studies); hypotension (seven studies); acute coronary syndrome (five studies); 30-day mortality (four studies); pain (three studies); pneumonia and time from injury to surgery (both two studies), being out of bed on the first post-operative day, orthogeriatric input (both no studies); and the three outcomes developed from PPI: mobility status and return to preoperative residence (both one study), and quality of life (no studies).

As the authors acknowledge, 66% (2550/3866) of the patients (and, therefore, of the evidential contribution to their results) were from the recently published RAGA and REGAIN (1) studies.[3,4] The authors did not include the pre-planned secondary analysis of pain, analgesic use and patient satisfaction ("REGAIN (2)"),[5] or any data from iHOPE, a similar, imminent, large RCT (n=1032).[6] Perhaps controversially, the authors excluded 24 studies (n=2680) published before 2003, effectively on the grounds of publication date rather than anaesthetic technique. However, these studies were included in the most recent Cochrane review on the same topic which drew similar conclusions (i.e., no difference),[7] so it is unlikely that the predominant evidential contribution from RAGA/REGAIN (1) would have been offset by a more comprehensive analysis (although an update of the Cochrane review appears due). Nevertheless, RAGA, REGAIN and iHOPE are three of the largest trials examining anaesthetic mode and outcomes after hip fracture surgery, together contributing approximately three-quarters of patients amongst recent RCTs, and are likely to influence the perceptions of anaesthetists, surgeons, patients, and their families for years to come. It is imperative, therefore, that readers understand the strengths and weaknesses of these studies. In this editorial, we consider the relevant methodological features of these influential studies and suggest how their findings may influence practice and future research.

Summary characteristics of the three trials (RAGA, REGAIN 1 and iHOPE) are shown in table 1, and the primary and secondary outcomes are shown in table 2.

(**Table 1**. Summary of the recruitment and patient characteristics, and sample size calculation)

(**Table 2**. Summary of the primary and secondary outcomes, results and authors' conclusions)

The clinical, financial and organisational effort involved in conducting these large, modern, pragmatic, multicentre RCTs (and reporting them in high impact peer-reviewed journals) should not be underestimated, and we thoroughly commend the patients and researchers for their efforts. Researchers have responded quickly to calls to conduct such RCTs,[7-9] and secured an impressive amount of funding to conduct them appropriately (e.g., US$ 12 million for REGAIN, equivalent to US$ 7500 per patient enrolled), which indicates the importance of the questions being asked. The 2016 Cochrane review noted the relative dearth of quality evidence in this area, concluding: "*large randomized trials reflecting actual clinical practice are required before drawing final conclusions*".[7]

Taken at face value, Kunutsor and colleagues' results (based mainly on RAGA and REGAIN) should encourage anaesthetists to accept that *there may genuinely be no difference in outcome* between patients administered SA versus GA for hip fracture surgery.[1] An alternative, but closely related, interpretation is one that challenges professional hubris: although the importance of anaesthesia in patient care is embedded in anaesthetists' professional identities, it is possible that anaesthesia (and anaesthetists) may have only minimal effects on commonly measured outcomes.[10] Other complex, causally dispositional factors, including major surgery, orthogeriatric care, organisational variables and patient factors (e.g. age, comorbidities, frailty, polypharmacy) may simply be more important - excepting catastrophic anaesthetic incidents, which appear rare during hip fracture surgery (one-day mortality is approximately 0.5%).[11]

However, we consider that it is more likely that outcome differences *do* exist between SA and GA - particularly amongst patients who are older, frailer, more co-morbid, are taking anticoagulants,[12] and / or have impaired cognition, but conceptual and methodological problems persist in the design and conduct of RCTs in this population that can obscure their detection. We discussed these problems in an editorial published a decade ago,[8] and these have since been acknowledged by the authors themselves,[3-5] by Avidan and colleagues in two associated editorials,[13-14] and more recently by Hadzic in a fiery online critique of REGAIN.[15] In no particular order, these problems relate to equipoise, selection bias, choice of outcomes, intervention definition, technical competence, and are manifest by comparison to the results and conclusions of contemporary large registry-based observational studies and mixed methods meta-analysis which have (admittedly, inconsistently) reported outcome benefits after SA compared to GA for hip fracture surgery.[11,16-20] This is not to imply the superiority of any study type, but merely to highlight that factors other than study design need to be considered when evaluating RCTs in this area.[21]

Equipoise in data does not necessarily translate to equipoise in the mind of the practitioner, the culture of the institution, or national guidelines.[22] Lack of directive evidence has undoubtedly contributed to anaesthesia providers adopting the anaesthetic mode they are most comfortable administering and believe has the best outcomes, possibly regardless of patient choice in some cases. In the setting of RCTs, these implicit biases may result in

participants being preferentially assigned to the intervention which, in the opinion of the researchers or clinicians, is likely to confirm those beliefs. Furthermore, excluding those who are likely to have poorer outcomes can bias comparative analyses. Invariably, such biases are unintentional, but might be more likely, for example, when RCT intervention ratios (1:1) differ from historic ratios of anaesthetic mode (e.g., SA:GA 1:2.3 in New York, US),[4,5,20] or when a large proportion of patients presenting to hospital with hip fracture are ineligible for trial participation, even if for valid, predetermined reasons.[4,5]

Selection biases in RCTs may create similar confounding factors to those traditionally criticised in observational studies, and may have impacted RAGA and REGAIN; the demographic data in both studies indicate a population that is fitter, more independent, and (in the case of REGAIN) younger than in representative observational samples.[3-5,11,18,20] Patients recruited to REGAIN (only 7.4% of those screened) had a mean age of 78 years, ~65% were ASA III or IV, and 92% lived at home or in a retirement home before their injury.[4] Patients recruited to RAGA (43% of those screened) had a median age of 77 years, only ~20% were classified as ASA III or IV despite a ~40% prevalence of pre-existing dementia,[3] and of the 942 patients included in the analysis, 63% were from a single hospital.[3] Neither study reported the frailty status of their participants. Recent database studies have reported mean ages of 83 (US and UK)[20,23] and 77 (China)[24] years. In England and Wales, 67% of patients with hip fracture are classified as ASA III+ (~84% having at least one comorbidity)[23], ~83% are admitted from their own home (including sheltered housing) and ~20% have pre-existing dementia.[23,25] Individually, these may be dismissed as small variations, but their intersectionality often results in the trial exclusion of potential participants with the highest risks of poor outcomes for whom we need to define the safest care (e.g., very elderly ASA IV patients with dementia who are taking anticoagulants).

Meta-analysis can magnify selection biases. Kunutsor and colleagues' total sample represents the equivalent of just 4.6% of the annual UK hip fracture population,[1] or 1.2% of the USA hip fracture population (only 0.2% and 0.006% respectively over the 20-year period of their meta-analysis), so even minor biases might cause significant errors if generalised to a diverse population inclusive of older, sicker, frailer patients with more advanced cognitive impairment. Randomisation can reduce selection bias but does not necessarily nullify it altogether. Instead, and for example, a cluster cohort trial design could be used to reduce bias (and may have delivered different results for the primary outcomes used in REGAIN and RAGA). Using this methodology, the intervention is administered to patients at each study site for a limited time period (e.g. one month GA, next month SA). In the context of hip fracture anaesthesia, informed patient consent may not be required as both interventions constitute 'standard-of-care'.[25, 26] Exposure in each hospital is based only on time period rather than patient characteristics, and all eligible patients receive the designated intervention, increasing enrolment by reducing selection bias (albeit potentially increasing crossovers between intervention groups). [27, 28]

Related to this, both REGAIN and RAGA may have recruited only half the number of participants that might have been needed to detect statistically significant differences in primary outcome if they had occurred. Leaving aside the problems of using composite outcomes and drawing conclusions from unpowered secondary outcomes,[29,30] the observed primary outcome in both studies occurred at approximately half the expected rate of incidence (REGAIN ~34% vs. 18%, RAGA 17% vs. 6%).[3,4] Furthermore, sample size characterisation and inclusion in statistical analysis were further confused by crossovers between groups: in REGAIN, for example, an intention-to-treat analysis was performed, but 119/785 (15%) of patients assigned SA received GA, and 28/797 (4%) assigned GA received SA.[4]

In spite of these issues, we do not believe that more robust sample sizes would have affected the results, or the authors' conclusions, for three further reasons. Firstly, the primary outcomes of both studies, although measurable, definite and (commendably) important to patients,[2,31] are unlikely to have been affected specifically and sufficiently by anaesthesia (i.e., a two-hour intervention) at the time horizons chosen for their quantification (i.e., 7 or 60 days later). Secondly, the broad, binary categorisation of patients into 'spinal/regional' or 'general' anaesthesia obscures a wide variety of interventions and techniques including differing drugs, doses, monitoring, and analgesic approaches, to name but a few, each subcategory of which may influence different patient outcomes (both within groups (e.g., SA vs. SA with sedation) and between (e.g., SA without nerve block vs. GA with nerve block)). For example RAGA (but not REGAIN) included data on (relatively large) doses of intrathecal local anaesthesia (equivalent median 2.8mls 0.5% ropivacaine), administered most commonly as part of a combined spinal-epidural technique (73%) without sedation[3], contrasting with standard care in the US and UK.[11,20] Thirdly, technical expertise may have influenced SA outcomes more than GA:[15] patients in RAGA were anaesthetised by more junior anaesthetists than might be expected in other settings,[3,32,33] and failure of SA occurred three times more frequently in REGAIN than in similar work from the UK (8% vs. 3%, respectively),[4,11] where SA is administered more frequently than in China or the US.[20]

Taken together, these factors support our previous assertion that a very large RCT (~11,000 participants per group) would be required to detect a statistically significant difference in any primary outcome measured beyond five postoperative days between anaesthetic modes for hip fracture surgery, particularly if enrolment rates are low, samples are unrepresentative, trials are unblinded and crossovers occur between groups.[8] Accordingly, we consider that ever bigger, more expensive, better-designed RCTs of RA vs. GA represent the wrong direction of travel for future research. Instead, we support the recommendations of the International Fragility Fracture Network (endorsed by the Association of Anaesthetists) and the James Lind Alliance priority setting partnership on fragility fractures of the lower limb,[9,32-33] to move the research agenda from *what* anaesthetic intervention is delivered to *how* it is delivered.[21] In short, this involves identifying best practice within each type of anaesthesia and then comparing appropriate outcomes between those best

practices.[2,34] Unless and until anaesthetic techniques are standardised *between* hospitals, we suggest that anaesthetists standardise technique *by* hospital (and according to informed patient choice),[35] agreeing to deliver anaesthesia in a consistent manner to improve the predictability (and so, management) of any associated side-effects or complications for providers of postoperative care (e.g., ward nurses, orthogeriatricians, physiotherapists, occupational therapists).

The results reported by Kunutsor and colleagues provide reassurance that mode of anaesthesia probably has very little influence on the outcomes commonly measured among the general hip fracture population, as recognised by professional guidance.[1] Researchers and clinicians should focus on the recommendation proposed in that guidance "*Anaesthesia should be administered according to agreed standards at each hospital, using age appropriate drug doses, with the aims of facilitating early patient remobilisation, re-enablement and rehabilitation*".[32] It is time to move beyond researching whether regional or general anaesthesia is better for hip fracture patients, and ask instead how we can deliver peri-operative care that helps shift patients' recovery trajectories from 'stay in bed, stay ill, stay in hospital' towards 'get up, get better, get home'.

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