'Ten'der points of perioperative analgesia research

Considerable research output in the field of anesthesiology is centered around perioperative analgesia practices. As a matter of fact, a PubMed search on "postoperative pain" generates results over 5,000 articles per year for the last decade. The colossal research magnitude pretty much bespeaks the extent to which this topic engages the fraternity. Moreover, "postoperative pain" is frequently linked to a range of keywords like "analgesia," "nerve block," "regional anesthesia," "surgery," "opioids," and "anesthesia" (bibliometric network analysis, Figure 1), simultaneously pointing toward a closely interconnected research frame, where the corresponding intricacies may compound the most meticulously planned endeavors in the subject. Hence, an opportune discussion follows, focusing on the 'ten'der points of the current analgesic literature which would warrant a careful reconsideration in future investigations.

(i) *Multimodal: the principle in place?*:- While novel loco-regional analgesic interventions continue to surface, the importance of individual mechanistically distinct components of an optimal and a "truly" multimodal analgesic plan can certainly not be undermined. In this context, a very recent 2023 scoping review by Mija *et al.*[1] deserves mention. The authors outline that as many as 9 out of every 10 randomized controlled trials (RCTs) evaluating regional analgesic techniques for mastectomy, failed to administer routine analgesics (paracetamol, non-steroidal anti-inflammatory drugs, etc.) in the comparator RCT limb.[1] Considering the well-established role of these analgesics in a multimodal regime, the concerns surrounding the denial of the former to the comparator group patients remain far more from nurturing the benefits attributable to the emerging analgesic modalities.

(ii) *Studying the right outcomes?*:- As the intricate research domain of perioperative analgesia evolves, it becomes pivotal to aim for a concomitant improvement in patient-reported outcomes (the role of which has been increasingly recognized over the past decades amidst declining anesthesia-related mortality and major morbidity). Having said that, as per a systematic review by Liu and Wu, the modest reductions in the postoperative pain scores (usual primary study objectives in analgesia research) do not necessarily translate into a better quality of recovery, patient satisfaction, or for that matter, the overall quality of life.[2] The aforementioned indeed serves as a clarion call for developing and validating patient-reported outcomes, where it be emphasized that mere inclusion of the Quality of Recovery–15 (QoR-15) scores does

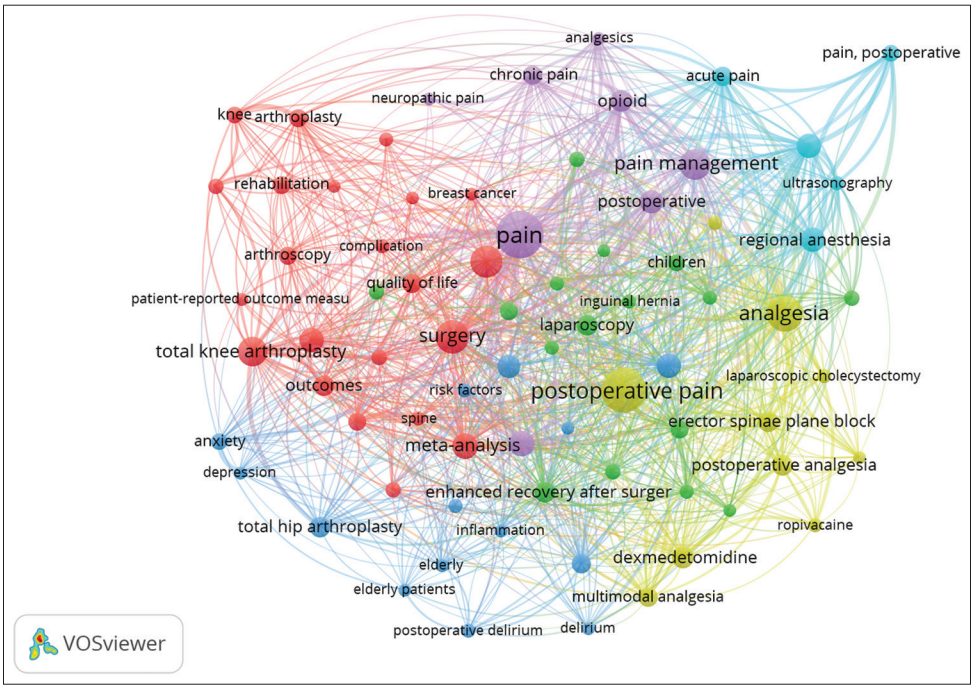

Figure 1: Bibliometric Network Visualization Analysis, using VOSviewer®, of the author keywords identified in connection to PubMed search keyword "postoperative pain"

not serve the purpose till the research endeavors are specifically designed and powered to detect clinically significant differences in the recovery profile.[2,3] Additionally, the cross-cultural adaptation of QoR-15 questionnaires employed to assess recovery makes for a concurrent research caveat in the purview of perioperative settings.[3]

(iii) *Unmet need to harmonize the regional nomenclature*:- The discussion quite naturally progresses to how often regional blocks (novel in technicalities or at times, in nomenclature) happen to materialize, to be closely followed by a series of evaluations of their perioperative applications and efficacy. Acknowledging the diversity in the regional analgesic vocabulary, the American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anesthesia and Pain Therapy (ASRA-ESRA) Delphi consensus recommends employing a standardized anatomically-descriptive nomenclature for research purposes.[4] Albeit the recommendations strive for larger objectives like streamlining the allied research, aimed at improving education and then ultimately patient care, it is found that the conventional and, in some instances, misleading regional vocabulary continues to be followed despite sufficient time having elapsed ever since the commencement of the ASRA-ESRA nomenclature harmonization initiative.[4,5]

(iv) *Intraoperative nociception monitoring*:- The sensitivity-specificity of monitoring nociception under general anesthesia by clinical signs, such as hypertension and tachycardia has been interrogated for long.[6] It is likely for this reason that comprehending the autonomic and electroencephalographic responses to noxious stimuli is now being ardently pursued.[7] That said, till the time we come to have routine access to validated analgesia nociceptive indices, the intraoperative reliance on hemodynamic surrogates of pain should be even carefully backed by accommodating the clinical context while ensuring a close surveillance for an adequate depth of anesthesia in the analgesia research endeavors.[6,7] Nonetheless, there also remain many unanswered questions as to what our approach should be to intraoperative nociception monitoring in high-risk patients on cardiopulmonary bypass, heart blocks, arrhythmias, implanted pacemakers, etc. The former as highlighted in an Editorial by Daccache *et al*., is further perpetuated by the pressing need for developing a personalized approach to titrate opioid-analgesia intraoperatively, particularly in the era of tumultuous debates on opioid-related adverse effects (ORADES) owing to which opioid-sparing (to the extent of totally excluding opioids intraoperatively in the name of opioid-free anesthesia) is being researched for feasibility across every possible opportunity and capacity.[6,8]

(v) *Sham, to be shamed?*:- Blinding constitutes an integral component of RCTs in perioperative analgesia research, given a possible "Pygmalion effect" working at the level of the investigator. Of note, achieving double-blinding by blinding the investigator can be challenging short of employing a block with nil therapeutic effects (for instance, an equivalent saline injection instead of the local anesthetic drug). Herein, the ethical concerns emanating because of exposing the control group patients to the potential risks of "needling" for nil-null regional blocks, make for a parallel argument where the inclusion of sham block is precariously placed at the crossroads between robustness and ethics in the perioperative analgesia research.[9]

(vi) *The process of opioid-reporting*:- Needless to say, alongside pain scores, opioid requirements feature as pertinent study objectives in the perioperative analgesia literature, all the more when concerns surrounding ORADES only seem to be intensifying.[8] To that end, comprehension of opioid consumption in RCTs can be aided by resorting to uniform metrics, such as morphine equivalents (ME). The latter can potentially control for varying strengths of the opioids under examination in a single research frame.[10]

(vii) *Finding clinical meaningfulness amid statistical significance*:- The inferences of RCTs in the pain research hinging on statistical significance might not necessarily imply clinical significance. This brings the requisite attention to the concept of minimal clinically important difference, i.e., the MCID. With MCID denoting the smallest change in the outcome under evaluation that the "patient would" and we as "researchers should" perceive to be clinically significant, a systematic review by Laigaard *et al*.[11] having included 570 trials, revealed an absolute reduction of 10 mg intravenous morphine in 24 hours as the MCID in settings of total hip arthroplasty. Similarly, MCID was outlined by the research group for the pain scores as well (an absolute reduction of 15 mm at rest and 18 mm during movement on a 0–100 mm Visual Analog Scale).[11] Thus, the fact be buttressed that the RCTs need to critically apprise their statistically significant results in the light of the corresponding MCID, for the given clinical setting.

(viii) *Heterogeneity, an Achilles' heel?*:- It has almost been a decade now since an elaborate review by Espitalier *et al.*[12] emphasized that the meta-analyses focusing perioperative pain ought to explore the

clinical heterogeneity linked with the nature of the surgical intervention, particularly given the understanding the clinical guidelines are premised on these meta-analyses. Withstanding, collaborative endeavors as portrayed by the Procedure-Specific Pain Management (PROSPECT), provide for evidence-based recommendations designed to accommodate for the perioperative periods of pain on a procedure-specific basis.[13] The formulation of PROSPECT guidelines is a reassuring step in the direction of overcoming the practical implications of heterogeneity.[12,13]

(ix) *Analgesic research in retrospect, of any good?*:- Having discussed the roadblocks in the conduct of perioperative analgesia RCTs at length, it does not remain difficult to interpret the problems, namely an assorted set of biases and confounding associated with analgesic research in retrospect. With more such retrospective literature being published, a thorough critical methodological appraisal is paramount to introspect the real-world value of research in retrospect (the findings of which should be used to lay the foundation for future prospective studies in the subject, at best).[14] To add to it, providing free-pass to the safety of the novel regional techniques premised on retrospective studies (not formally designed to study the set of potential complications in predisposed settings) is not without its' own peculiar concerns.[15]

(x) *Perioperative analgesia research as hotspots of retracted literature?*:- Finally, any research is closely knitted around building a base of sound bibliography. A worrying trend as revealed in a contemporary example by De Cassai *et al*.[16] is presented by the rather frequent phenomenon of the citation of retracted literature in regional anesthesia. This mandates the fraternity to reflect if regional literature is developing as a potential hotspot of retracted literature and regardless, combative measures should be ensured to prevent citation of such work to preserve the integrity and veracity of our perioperative analgesia research ecosystem.

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