Off-label use of drugs in regional anesthesia: A need for setting up policies

Many adjuvants in neuraxial or perineural anesthesia lack sufficient evidence for their safety, as also authorized licensing from competent authorities around the globe. Most of these additives were initially approved for systemic use though later found to be reliable and safe in regional blocks; thus propagating their off-label use. Research is continuously being updated, and numerous studies have mentioned the efficacy of these additives through various routes, thus flooding the literature.

Further, it may come as a surprise to many anesthesiologists that even the adjuvants such as midazolam, magnesium, ketamine, dexmedetomidine, clonidine, or various opioids that we have been using routinely were never approved for perineural use. This may further ignite a question in our minds, “Is the practice of using these drug solutions for regional anesthesia unethical?” or “Can we be implicated legally in the face of any complication following their use in neuraxial blocks?”

With decades of “safe anesthesia” slogan, how and why did this all start. Silently, these drug solutions have crept into our practice and now have become an imperative practice. The compelling reasons may include prolongation of anesthesia, postoperative analgesia, hemodynamic stability, chronic pain, and palliative care. Over and above, once one adjuvant gets Food and Drug Administration (FDA) approval (e.g., injection clonidine for epidural route), anesthesiologists tend to use the other adjuvants (e.g., injection dexmedetomidine) sharing the same class. This leads to the bypass of the toxicology, animal studies, and Phase 1 trials of FDA. Many a times, this practice is not even clinically registered or audited; thus, the side effects if any observed, may also not get reported by the clinician. Over and above, the research protocols involving the use of these drugs perineurally may obtain approval fortuitously due to ignorance on the part of Ethical Committee. The FDA approval for using drugs in such new indications or disseminating information regarding the same requires supplemental drug application to be filed by the pharmaceutical company. This process is very expensive and time consuming; moreover, it does not extend any benefit to the proprietor. Therefore, the drug continues to be in the market, and the indications inscribed on the label never get revised.[1,2]

The risk of neurotoxicity posed by such off-label usage may not be evident frequently in the minute concentrations generally administered. Most of the drug trials are conducted to test the analgesic efficacy of the off-label drugs and do not have enough power to detect the side effects. However, in a higher dose, tramadol injected intrathecally has reported to produce grave neurological, respiratory, and hemodynamic sequel.[3,4] Even worse are the reports of high-dose long-term opioids’ (morphine, hydromorphone, and tramadol) infusions leading to intrathecal granuloma formation presenting as sensory and motor deficits.[5] Therefore, before administering these adjuvants in regional anesthesia, laboratory studies and animal testing should be conducted again since the primary approval was attained for systemic route only.

Despite that, the other side of tug is strongly pulled by extensive researches indicating safe performance of neuraxial additives, continuing their use in perioperative settings. Prolongation of analgesia by additives in surgeries involving thoracolumbar/sacral dermatomes has not only demonstrated their efficacy but also decrease in temporary side effects such as respiratory depression, urinary retention, and prolonged motor block. Over and above, the dearth of available and authorized alternatives can be illustrated by one of the above-mentioned cases of intrathecal granuloma, which after surgical excision, was resumed on intrathecal tramadol again for palliative care.[6] Thus, in the light of the absence of any attested recommendation, the clinician has to decide the risk–benefit out of available alternatives in each clinical scenario.

This clinical practice of using drugs for off-label indications and patient profile (e.g., pediatric, obstetric, and geriatric) can also invite serious ethical issues and legal implications. In
the absence of alternative options, perineural usage of these adjuvants may be well justifiable in indications involving palliative care and chronic unrelenting pains. This can be exemplified by the use of clonidine in paravertebral block and opioids through intraspinal route for chronic pains such as refractory postherpetic neuralgia.[6] The American Society of Health System Pharmacists recommends the judicious use of published evidence by the prescriber who holds the ultimate responsibility of safety and efficacy.[7] Furthermore, such information should only be drawn from standard peer-reviewed journal managed by an organization with an editorial board with experts in the subject of the article.[2,8]

Legal proceedings in case of any suite may, however, make the physician vulnerable in the absence of informed consent or proved negligence.[1] This informed consent may not require detailing of off-label use in case of drugs which have strong evidence of their use or a part of standard practice such as epinephrine, phenylephrine, clonidine, and neostigmine for central neuraxial blocks and epinephrine, clonidine, opioids, and ketamine for nerve blocks.[9] For drugs lacking scientific database, informed consent also needs to be complemented with Investigational New Drug Application registered under an authorized body.[10] This may include potential adjuvants drugs such as adenosine, calcium channel blocker, calcitonin, and cannabinoids receptor agonists.

Nowadays, more and more international journals are framing their policies regarding publication of scientific researches on off-label uses. This includes Ethical Committee approval, informed consent, and above all, supporting scientific evidence. In addition to these, research protocols unsupported with adequate evidence need justification for safety of off-label usage, information on existing animal and human neurotoxicity, and clear description of conditions, in which the trial was conducted.[10,12]

Clinicians, researchers, and government should join hands to generate evidence for safety and efficacy in use of drugs for nonapproved indications. Reporting and publishing of critical incidents with off-label use at scientific platforms may guide the optimal use with minimized complications. Compilation of evidence in the form of systematic reviews and meta-analysis can help making decisions in individual case scenarios based on the safety of various routes and doses of these drugs. Recent research on the role of clonidine, dexmetsadone, buprenorphine, and dexmedetomidine in perineural analgesia describes the safety, effectiveness, side effects, and optimal doses of these adjuvants.[13-15] Apart from describing the safe potential use according to clinical condition, such systemic reviews also serve as lighthouses for anesthesiologists and algologist in demarcating potential areas of research.

Above all, the approval extended by the FDA should also be for a stipulated time, following which the pharmaceutical companies will compulsively have to recollect the scientific data. Thus, drug distributors will also participate, and the indication, route of administration dosage, or side effects reflected in the label would periodically get updated. These team efforts can help improving the patient as well as legal safety in anesthesia practice.

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