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A Mini-review on the Necessity of Expanding Personalized Medicine for the Future of Various Aspects of Pain Management

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Abstract

Pain is recognized as a deeply personal, psychological, and social sensation, the perception of which is influenced by diverse factors. The intensity and nature of pain vary among individuals, rendering pain a highly personal phenomenon that warrants tailored approaches. Precision medicine is a therapeutic paradigm grounded in the evaluation of multiple patient-specific factors, including environmental factors, lifestyle, and genetic variations, to determine the most suitable treatment approach for each individual. Research indicates that certain genetic variations can influence how individuals experience and respond to pain. While there is limited evidence in leveraging genetic testing results to tailor treatment approaches, recent years have shown promising outcomes in managing surgical pain or pain associated with opioid use or cessation.

Keywords: Personalized Medicine, Pain, Anesthesia

1. Context

1.1. The Role of Personalized Medicine

In the past century, as understanding of the human genetic map has advanced, healthcare professionals have increasingly recognized the importance of tailoring treatment to individual characteristics. Consequently, there has been a focus on developing projects aimed at optimizing health outcomes based on an individual's genetic makeup. Studies examining the genetic profiles of various individuals have revealed that over 99% of genetic composition is shared among humans, with the remaining fraction accounting for differences between individuals. It is evident that variations in genetic makeup play a significant role in how individuals respond to different medications (1). Therefore, it is essential to address the therapeutic and medicinal needs of each individual by considering their unique genetic profile. In essence, personalized medicine entails creating individualized treatment plans for managing pain sensitivity and metabolism based on genetic variations in patients. This approach can facilitate the treatment of patients with distinct needs and pave the way for innovative approaches to managing acute pre-surgical pain.

Today, pharmacogenetics is recognized as a science that investigates the differences between individual alleles of genes and the varied responses of patients to drugs (2-4). A range of pharmacokinetic and pharmacodynamic genes can predict patients' experiences before surgery and postoperative pain complications. Various genetic variants are factors that determine the metabolism of analgesics in patients. Following the deaths of several pediatric patients undergoing tonsillectomy surgery in 2012, the US Food and Drug Administration expressed concerns about the use of codeine as a pain control medication in a report (5). Subsequent investigations revealed that the cause of death was codeine overdose and the rapid conversion of

codeine to morphine, with codeine-induced toxicity influenced by genetic variations in CYP2D6. Consequently, specific guidelines have been developed for interpreting genetic test results to determine the appropriate use of pain relievers such as codeine and other analgesic medications (5-10). Genetic variability can impact the efficacy of drugs and the effectiveness of multimodal treatments and other analgesics. Scientists have identified over 400 genes whose variability can affect patients' analgesic metabolism and their response to prescribed pain management treatments. Moreover, research has explored genetic mechanisms that influence the pain experience process (11, 12). Examples include polymorphic variations in genes such as the vanilloid receptor subtype 1, μ-opioid receptor, catechol-O-methyltransferase, and opioid receptor delta subtype 1 (13-18). Additionally, certain gene variants that encode pain receptors and neural mediators, such as SCN9A, MC1R, GCH1, and 5-HTTLPR, can affect a patient's sensitivity to pain (19). Previous studies have investigated genes involved in amplifying the intensity of pain experienced due to trauma and chronic pain conditions. Pharmacogenomic analysis offers the possibility of examining a patient's entire genome and identifying genes that influence their response to pain relievers (20).

During surgery, two groups of neuromuscular blocking agents are utilized as adjunctive anesthetic drugs, classified based on their function. Non-depolarizing drugs act as competitive antagonists of the nicotinic acetylcholine receptor and include vecuronium, rocuronium, mivacurium, and [cis] atracurium. Depolarizing drugs mimic acetylcholine's role, leading to muscle cell membrane depolarization and receptor desensitization. Suxamethonium or succinylcholine is an example of such blocking agents (21). While all these neuromuscular blocking agents consist of quaternary ammonium compounds, their distinct clinical applications stem from structural differences. For instance, vecuronium and rocuronium, both potent neuromuscular blockers, feature two quaternary ammonium cations, while (cis) atracurium contains one quaternary cation and a tertiary amine. Protonation of the amine in acidotic patients increases the drug's positive charge, rendering vecuronium and rocuronium more potent than other blockers (22-24). Despite their utility, these drugs have limitations. Vecuronium should be cautiously administered to burn patients or those with kidney disorders (25). Additionally, the degradation rate of (cis) atracurium is influenced by Hofmann elimination and ester hydrolysis, minimizing drug wastage under conditions of decreased body temperature and pH (26). Rocuronium undergoes biliary excretion, regulated by hepatocyte uptake via anion-transporting polypeptides OATP1A2 and OATP1B1 (27). The function of these transporter receptors is heavily influenced by genetic polymorphism, impacting drug performance. Recent studies have explored the effect of genetic polymorphism on the pharmacokinetics of these neuromuscular blockers. Costa et al. discovered that the T/del genotype decreases rocuronium clearance compared to del/del genotypes, with SNP rs3834939 in the OATP1A2 coding gene influencing rocuronium elimination (24). Investigation into the role of gene polymorphisms encoding P-gp (ABCB1) and OATP1B1 (SLOB1B1) on rocuronium action revealed prolonged rocuronium recovery time in patients with ABCB1 rs1128503 TT and SLCO1B1 rs2306283 AG and GG genotypes, due to reduced hepatic removal (28). Some researchers suggest that gene polymorphisms encoding the alpha subunit of nAch, responsible for neuromuscular blocker binding and channel opening, also affect blocker action (28).

On the other hand, succinylcholine undergoes conversion into three components: Succinic acid, succinylmonocholine, and choline, catalyzed by the butyrylcholinesterase (BChE) enzyme. This liver-produced enzyme is absent in the synaptic cleft at the neuromuscular junction, resulting in a longer duration of action compared to acetylcholine, which is rapidly metabolized by acetylcholinesterase in the neuromuscular junction (29). Research indicates that certain individuals, such as those with diabetes, obesity, high-protein diets, uremia, and hyperlipidemia, exhibit higher activity and plasma levels of the butyrylcholinesterase enzyme. Conversely, acute inflammation, severe stress, nutritional imbalances, cardiovascular diseases, and certain types of cancer can lead to decreased plasma levels of this enzyme (30).

The butyrylcholinesterase enzyme is polymorphic, with 62 SNPs identified in the coding region. Mutations and polymorphisms in this enzyme lead to reduced activity, resulting in prolonged suxamethonium activity, potentially causing apnea and extended paralysis (28). The most notable mutations in this enzyme include:

- Atypical: Creation of the A-variant and dibucaine resistance

- Kalow: Creation of the K-variant

- Fluoride: Creation of the F-variant

- Silent: Creation of the S-variant

The diversity and prevalence of these mutations vary among individuals, with studies indicating that the K-variant (rs1803274) and A-variant (rs1799807) are more common in the white population. Additionally, in

heterozygous individuals with the A-variant, the drug's effect is significantly heightened, while in homozygous individuals, the drug's effectiveness is 60 times higher than in others (29). In many instances, the activity of the butyrylcholinesterase enzyme is diminished in the F-variant (SNP rs28933390) and K-variant (SNP rs1803274) (31). Among these variants, the S-variant is the rarest and most perilous type, observed solely in individuals of Indian descent (28). Furthermore, researchers have identified that succinylcholine (SCH) and volatile anesthetics' immunity can be altered by one of the 50 polymorphism types of CACNA1S and RYR1 genes. In patients with muscular disorders stemming from alterations in these genes, SCH consumption is not recommended due to heightened sensitivity to malignant hyperthermia (MH) (32).

In the future, personalized medicine may enable physicians to assess patients' pharmacogenomic information and pain sensitivity using a simple swab sample from the mouth. Consequently, tailored and precise treatments can be designed based on each patient's individual characteristics and advancements in genetic science. This approach allows for the identification of alleles associated with heightened pain sensation and the impact of pain intensity resulting from changes in pharmacokinetic and pharmacodynamic genes. Physicians can then adjust and optimize analgesics or mitigate their side effects accordingly. Another benefit of personalized medicine is the guidance it provides to doctors through pre-operative laboratory assessments, directing them towards the most suitable and genetically compatible treatment pathway for each patient to manage and alleviate pain.

Identifying the association between genetic variability and pain, as well as surgical patients' responses to analgesic agents, necessitates further clinical studies to better align patient care with personalized medicine. Genetics and related sciences are advancing rapidly, and it is conceivable that in the next few years, the assessment of the relationship between genetic susceptibility and pain response will become a routine part of clinical procedures before surgery.

2. Conclusions

Currently, treatment utilizing multimodal analgesia is the standard approach to pain management post-surgery. Research into the genetic mechanisms underlying pain paves the way for the development of individualized and more specialized treatments. In the forthcoming years, personalized medicine will take precedence as the preferred approach for researchers and physicians in managing clinical procedures in medical centers, supplanting current methods like multimodal analgesia. Additionally, it is noteworthy that the evaluation of non-pharmacological nursing interventions can significantly contribute to the monitoring and management of pain with the aid of genetic test results.

Footnotes

Authors' contribution: Mastaneh Dahi Taleghani, and Mohammad Reza Moshari: Visualization, investigation; Reyhaneh Zahiri, and Seyed Bashir Mirtajani: Supervision; Maryam Vosoughian: Conceptualization and review.

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