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Pharmacodynamic Mismatch in Adductor Canal Blockade: Dexamethasone Phosphate (Rapid-Salt) Outperforms Methylprednisolone Acetate (Depot-Suspension) for Early Mobilization

Beny Firmansyah[1*], Taufiq Agus Siswagama[2], Buyung Hartiyo Laksono[2]

[1]Resident of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia

[2]Supervisor, Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia

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***Corresponding author:**
Beny Firmansyah

E-mail address:
bennsyah29@gmail.com

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A B S T R A C T

Introduction: The motor-sparing adductor canal block (ACB) is central to enhanced recovery after surgery (ERAS) protocols for knee surgery. Corticosteroid adjuvants are used to prolong analgesia, but a direct comparison of perineural Dexamethasone and Methylprednisolone is lacking. This study aimed to observe real-world associations between these adjuvants, postoperative pain, and functional recovery. **Methods:** This analytical, prospective, observational cohort study was conducted at a tertiary hospital from November 2024 to April 2025. Fifty-three patients undergoing knee surgery under subarachnoid anesthesia were enrolled. Following surgery, patients received an ultrasound-guided ACB with 20 mL of Ropivacaine 0.5% combined with either Dexamethasone 10 mg (n=24) or Methylprednisolone 60 mg (n=29), based on the attending anesthesiologist's preference. The primary functional outcome was time to mobilization. Secondary outcomes included Numerical Rating Scale (NRS) pain scores at 12, 24, and 48 hours. **Results:** A significant association was observed for the primary functional outcome: 87.5% of the Dexamethasone cohort mobilized within 24 hours, versus 62.1% of the Methylprednisolone cohort ($p = 0.037$). This functional advantage was congruent with a superior early analgesic profile; the Dexamethasone group reported significantly lower mean NRS scores at 12 hours (2.71 ± 0.81 vs. 3.86 ± 1.13; $p < 0.001$) and 24 hours (2.17 ± 0.56 vs. 3.24 ± 0.69; $p < 0.001$). A significant baseline difference in age distribution ($p = 0.009$) was identified as a key variable. **Conclusion:** This study provides the first clinical comparison of a rapid-acting salt (Dexamethasone Phosphate) versus a depot-suspension (Methylprednisolone Acetate) as perineural adjuvants in ACB. The observed superior functional and analgesic profile of Dexamethasone aligns with its pharmacokinetic properties, suggesting a pharmacodynamic mismatch between slow-release formulations and the pathophysiology of acute 24-hour postoperative pain.

1. Introduction

Major knee surgery, encompassing procedures from total knee arthroplasty (TKA) to complex ligamentous reconstructions such as anterior cruciate ligament (ACL) repair, constitutes a significant and growing component of orthopedic practice.[1] While these interventions offer profound improvements in quality of life, their success is intrinsically linked to the management of the perioperative period.[2] The intense acute postoperative pain associated with these

procedures is a primary determinant of patient morbidity. This pain response, driven by surgical trauma and a cascade of inflammatory mediators, serves as a principal barrier to early patient mobilization, inhibits effective participation in physiotherapy, and is a key risk factor for developing complications such as venous thromboembolism (VTE), atelectasis, muscle atrophy, and persistent postoperative pain.[3] In response to these challenges, perioperative care paradigms have evolved significantly, shifting towards the principles of enhanced recovery after surgery (ERAS). A central pillar of ERAS in orthopedic surgery is the implementation of a sophisticated, multimodal, opioid-sparing analgesic regimen.[4] By combining multiple agents and techniques (such as neuraxial anesthesia, peripheral nerve blocks, and non-opioid analgesics) that target different nociceptive pathways, this approach aims to provide synergistic analgesia while mitigating the well-documented side effects of systemic opioids, such as sedation, respiratory depression, postoperative nausea and vomiting (PONV), and ileus.[5]

Within this multimodal framework, peripheral nerve blocks (PNBs) have been elevated from an adjunctive technique to a cornerstone of postoperative pain management for knee surgery.[6] The Femoral Nerve Block (FNB) was historically considered the standard of care, providing potent analgesia to the anterior knee. However, its utility in a modern ERAS setting is severely limited by its significant drawback: the unavoidable blockade of motor branches to the quadriceps femoris muscle. This iatrogenic motor weakness results in an unacceptably high risk of patient falls and directly contravenes the ERAS goal of immediate postoperative ambulation.[7] This limitation led to the widespread adoption of the adductor canal block (ACB). The ACB, a motor-sparing technique ideally performed under ultrasound guidance, targets the saphenous nerve (the terminal sensory branch of the femoral nerve) and, depending on the volume and proximal spread, the nerve to the vastus medialis, within the adductor canal in the mid-thigh. By primarily blocking the sensory innervation to the knee while preserving quadriceps motor function, the ACB provides a unique and powerful analgesic profile: effective pain relief that is fully compatible with early mobilization. Despite its clear advantages, the single-shot ACB, even with a long-acting local anesthetic such as Ropivacaine, has a finite duration of action, typically waning after 12 to 18 hours. As the block recedes, patients are highly susceptible to "rebound pain," a phenomenon characterized by a rapid and severe escalation in pain intensity that can abruptly halt recovery, induce significant distress, and increase opioid consumption. To mitigate this critical gap in analgesia, extensive research has focused on analgesic adjuvants capable of prolonging the block's duration.[8]

Of the adjuvants studied, perineural corticosteroids, particularly Dexamethasone, have emerged as the most effective and widely validated. When administered perineurally, corticosteroids are believed to prolong analgesia through at least two mechanisms: a potent local anti-inflammatory effect, suppressing the production of inflammatory mediators at the site of surgical trauma, and a direct, non-inflammatory neuronal effect, potentially suppressing ectopic nerve firing via glucocorticoid receptor-mediated changes in ion channel activity. While perineural Dexamethasone (Dexamethasone Phosphate, a rapid-acting salt) is well-established against placebo, another potent corticosteroid, Methylprednisolone, is also widely available and frequently used by clinicians in "off-label" applications for regional anesthesia and pain management.[9] Pharmacologically, these agents present a fascinating clinical dilemma. Dexamethasone offers exceptionally high glucocorticoid potency and a rapid onset of its anti-inflammatory action, making it theoretically ideal for blunting the acute inflammatory pain of the first 24 hours. Conversely, Methylprednisolone is often formulated as Methylprednisolone Acetate, a poorly soluble depot suspension designed for slow release and a much longer duration of local anti-inflammatory activity, as seen in intra-articular and epidural injections. This distinction presents a crucial, unanswered clinical question: for a single-shot PNB, is the fast-acting, high-potency Dexamethasone superior for managing the acute 24-hour pain window? Or does the long-acting depot profile of Methylprednisolone Acetate offer a more sustained benefit that better bridges the gap to effective oral

analgesia, potentially reducing pain at 48 hours and beyond? Despite the frequent pragmatic use of both agents in operating rooms worldwide, literature directly comparing perineural Dexamethasone to Methylprednisolone in a head-to-head fashion for ACB remains remarkably scarce. This evidence gap leaves clinicians to rely on pharmacological theory and personal preference rather than high-quality data to guide the optimal selection of a corticosteroid adjuvant.[10]

The primary aim of this study was to conduct a preliminary, pragmatic, observational investigation to address this gap in the literature. The primary objective was to explore the real-world association between the choice of perineural Dexamethasone versus Methylprednisolone as an adjuvant to Ropivacaine in ultrasound-guided ACB and the primary functional outcome of postoperative mobilization. The secondary aims were to explore the associations between the chosen adjuvant and postoperative pain scores (as reported on the Numerical Rating Scale) at 12, 24, and 48 hours, and the total length of postoperative hospital stay. The novelty of this investigation lies in its direct, real-world clinical comparison of two commonly available, yet pharmacologically distinct, corticosteroid adjuvants (a rapid-acting salt versus a long-acting depot suspension) within the specific, motor-sparing context of the ACB. While this observational study cannot determine impact or preference, its goal is to rigorously document these preliminary associations and serve a hypothesis-generating role. By focusing not only on pain scores but also on the critical, ERAS-driven metric of early mobilization, this research aims to provide the foundational data and methodological critique necessary to inform the design of a definitive randomized controlled trial (RCT).

2. Methods

This study was conducted as an analytical, prospective, observational cohort study at the Dr. Saiful Anwar Regional General Hospital, a tertiary academic medical center in Malang, Indonesia. The study design was chosen as a pragmatic, preliminary step to assess real-world practice patterns, evaluate outcome variability, and generate hypotheses for a future, more definitive RCT. We proactively acknowledge that this design is subject to significant limitations, most notably confounding by indication (selection bias). The study protocol was reviewed and approved by the Institutional Ethics Committee of Dr. Saiful Anwar Regional General Hospital, and the study was performed in accordance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment. Patients were prospectively enrolled between November 2024 and April 2025. Patients were eligible for inclusion if they met the following criteria: Age 16 years or older; Classified as American Society of Anesthesiologists (ASA) physical status I, II, or III; Scheduled to undergo elective knee surgery (including TKA, ACL/PCL reconstruction, meniscectomy, and other ligamentous repairs) under primary subarachnoid anesthesia; Willing and able to provide informed consent and participate in follow-up. Exclusion criteria were: Patient refusal to participate; Known allergy or contraindication to any of the study medications (Ropivacaine, Dexamethasone, Methylprednisolone, or bupivacaine); Pre-existing peripheral neuropathy, motor deficit, or significant chronic pain syndrome affecting the operative limb; Active infection at or near the intended block injection site; Significant hepatic or renal insufficiency (ASA IV or greater); Intraoperative conversion to general anesthesia; Any plan for postoperative admission to an intensive care unit (ICU); Incomplete or missing data for the primary or secondary outcome measures.

A non-probability quota sampling method was utilized. The sample size was estimated based on a power analysis for a two-group comparison. Based on institutional data and a review of the literature, we estimated a 24-hour mobilization rate of approximately 60% in the control (Methylprednisolone) arm. To detect a clinically significant 25% absolute improvement in this rate (85% mobilization) with an alpha of 0.05 and a power of 80%, the minimum required sample size was calculated to be 24 patients per group. To account for potential dropouts or data loss, the enrollment target was exceeded, and a final sample of 53 patients who met all criteria was included in the final analysis. The use of non-probability sampling is a recognized limitation that may affect the external validity

(generalizability) of our findings. All patients included in the study first received a standardized subarachnoid block for intraoperative anesthesia, consisting of 12.5 mg of hyperbaric Bupivacaine 0.5% injected at the L3-4 or L4-5 interspace. Following the completion of the surgical procedure, while still in the operating room, all patients received a postoperative analgesic Adductor Canal Block. Patients were allocated to one of two observational cohorts. Dexamethasone Group (Group D, n=24): Patients received an ultrasound-guided ACB with a total volume of 20 mL, consisting of Ropivacaine 0.5% combined with 10 mg of Dexamethasone Phosphate. Methylprednisolone Group (Group M, n=29): Patients received an ultrasound-guided ACB with a total volume of 20 mL, consisting of Ropivacaine 0.5% combined with 60 mg of Methylprednisolone Acetate. A critical, fundamental limitation of this observational study is the method of allocation. Group assignment was not randomized; rather, it was determined "per the attending anesthesiologist's preference." This method introduces a profound and unmeasurable risk of selection bias, or confounding by indication. This "preference" is not a random event; it is an active clinical decision likely based on a multitude of patient, surgeon, and procedural factors, both conscious and subconscious. For example, it is plausible that clinicians, perceiving Methylprednisolone Acetate as a longer-acting "depot" steroid, may have preferentially administered it to patients with higher anticipated inflammatory loads or pain (such as TKA versus ACL repair, or patients with pre-existing rheumatoid arthritis). Conversely, clinicians may have preferentially administered rapid-acting Dexamethasone Phosphate to younger, healthier patients undergoing less invasive procedures to facilitate same-day or next-day discharge. This non-random allocation hopelessly biases the two groups at baseline, and any unadjusted comparison between them is invalid.

To provide clarity on the interventions, all patients in Group D received 10 mg (2.5 mL of a 4 mg/mL solution) of Dexamethasone Phosphate (a water-soluble, rapid-acting salt). All patients in Group M received 60 mg (1.5 mL of a 40 mg/mL suspension) of Methylprednisolone Acetate (a poorly soluble depot suspension). The choice of these doses was a pragmatic approximation of systemic anti-inflammatory equipotency, based on standard glucocorticoid conversion charts (approximately 0.75 mg Dexamethasone ≈ 4 mg Methylprednisolone; thus 10 mg Dex ≈ 53.3 mg MP). We chose 60 mg of MP as a practical dose. We explicitly acknowledge that this systemic equivalence is an unproven assumption for perineural administration, and the true perineural dose-response relationship is unknown. Furthermore, we acknowledge that the 10 mg dose of Dexamethasone is at the high end of the 4-8 mg range, where a ceiling effect for perineural analgesia has been suggested in some studies.

All blocks were performed by one of three credentialed senior anesthesiologists to ensure technical consistency. With the patient in the supine position and the leg slightly externally rotated, a high-frequency linear ultrasound transducer (Sonosite, Inc.) was placed at the junction of the middle and distal third of the thigh. After aseptic skin preparation with chlorhexidine, the transducer was used to identify the sartorius muscle, the femoral artery, and the adductor canal deep to the sartorius. A 22-gauge, 100-mm block needle was advanced in-plane in a lateral-to-medial orientation. The needle tip was carefully positioned in the fascial plane of the canal, adjacent to the artery. After gentle negative aspiration for blood, the 20 mL study solution (as per group allocation) was injected in 5 mL aliquots with real-time ultrasound visualization to confirm appropriate spread within the canal.

Data were collected prospectively by trained members of the research team (not involved in the patient's direct care) via direct patient interviews and a thorough review of the electronic medical records, anesthesia charts, and physiotherapy notes. The primary outcome for this study was re-defined as the time to successful mobilization. Mobilization was defined as the patient's first documented successful attempt to perform a functional activity (such as sitting unsupported on the edge of the bed for 1 minute, standing with a walker, or ambulating with assistance) as documented by the physiotherapy team or nursing staff. This was categorized as a binary outcome: Early Mobilization (achieved within 24 hours of surgery

completion) or Delayed Mobilization (requiring > 24 hours). Postoperative Pain Intensity: Measured using the 11-point Numerical Rating Scale (NRS), where 0 represented "no pain" and 10 represented "the worst pain imaginable." Measurements were recorded at three fixed time points: 12 hours, 24 hours, and 48 hours postoperatively. Length of Hospital Stay (LOS): Calculated as the total number of postoperative days, with the day of surgery being day 0, until hospital discharge.

All data were encoded and analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL). Patient characteristics and outcomes were summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, and as frequencies and percentages for categorical variables. To describe the initial, unadjusted associations, we compared the two groups. For categorical variables (gender, procedure type, mobilization), the Chi-square test or Fisher's exact test was used. For continuous variables (age, NRS scores), independent samples t-tests or Mann-Whitney U tests were used as appropriate based on data distribution. A two-tailed p-value of < 0.05 was considered statistically significant for these initial comparisons. A multivariable analysis (such as logistic regression for mobilization or ANCOVA for pain scores) to statistically control for confounders was not performed. Such an analysis would be statistically invalid and scientifically misleading for two primary reasons: (1) the critical covariate of Rescue Analgeslgesic Consumption (OME) was not collected, making the NRS models impossible, and (2) the number of unmeasured confounders (BMI, baseline functional status, Diabetes status) tied to the non-random allocation was too high, meaning any model adjusting only for Age would be fatally misspecified. Therefore, we present only the unadjusted, descriptive data and interpret it with appropriate caution.

3. Results

A total of 53 patients who met all inclusion criteria were prospectively enrolled and included in the final analysis. Of these, 24 patients were allocated to the Dexamethasone (Group D) cohort and 29 patients were allocated to the Methylprednisolone (Group M) cohort. The demographic, clinical, and surgical characteristics of the two cohorts are presented in Figure 1. The groups were found to be statistically homogenous in their distribution of patient gender ($p = 0.817$).However, a statistically significant and clinically crucial difference was identified in the age distribution of the two groups ($p = 0.009$). The distribution analysis confirmed the Dexamethasone group had a high concentration of patients in the 30-39 year bracket (29.2%), while the Methylprednisolone group had a higher concentration of patients in both the 20-29 year bracket (31.0%) and the ≥70 year bracket (24.1%). This baseline imbalance in Age, a primary independent predictor of postoperative mobilization, represents a major confounding variable that fundamentally compromises any direct, unadjusted comparison of the study's functional outcomes. Furthermore, data for other important potential confounders, such as Body Mass Index (BMI), Diabetes Mellitus status, and baseline functional status, were not systematically collected.

The unadjusted analysis of postoperative pain scores, measured by NRS, is presented in Figure 2. In this preliminary comparison, the Dexamethasone group reported statistically significantly lower mean NRS scores at both the 12-hour and 24-hour time points ($p < 0.001$ for both). The mean difference at 12 hours was -1.15 (95% CI: -1.77 to -0.53), and at 24 hours was -1.07 (95% CI: -1.51 to -0.64). Both differences exceed the commonly accepted minimum clinically important difference (MCID) of 1 point for NRS. By the 48-hour time point, pain scores were low in both groups (mean 1.13 vs 1.03), and the difference was no longer statistically significant ($p = 0.219$).

The unadjusted analysis of the primary functional outcome (mobilization) and secondary LOS is presented in Figure 3. A Chi-square analysis revealed a statistically significant association between the adjuvant group and the time to mobilization ($p = 0.037$). A substantially higher proportion of the Dexamethasone group (87.5%) achieved early mobilization within 24 hours, compared to only 62.1% of the Methylprednisolone group. This finding, while striking, is confounded by the significant baseline difference in age ($p = 0.009$) and cannot be definitively

attributed to the study drug. Regarding the secondary outcome of postoperative length of stay, no statistically significant difference was found between the two groups ($p = 0.631$). The vast majority of patients in both cohorts (87.5% in Group D and 82.8% in Group M) were discharged on postoperative day 2, likely reflecting standardized institutional discharge protocols.

Baseline Patient Demographics and Clinical Characteristics by Regimen

A schematic crosstabulation of patient cohorts (Total N=53). In-cell bars represent the percentage of patients within each group.

Dexamethasone Group (n=24) Methylprednisolone Group (n=29)

Characteristic	Dexamethasone	Methylprednisolone
Age Group		p = 0.009
<20 years	20.8%	3.4%
20-29 years	4.2%	31.0%
30-39 years	29.2%	10.3%
40-49 years	12.5%	13.8%
50-59 years	8.3%	0.0%
60-69 years	20.8%	17.2%
≥70 years	4.2%	24.1%
Gender		p = 0.817
Male	58.3%	55.2%
Female	41.7%	44.8%
Type of Surgery		p = 0.865
ACL	45.8%	34.5%
PCL	12.5%	6.9%
TKR	25.0%	31.0%
Other	16.7%	27.6%

Figure 1. Baseline patients' demographics and clinical characteristics by regimen.

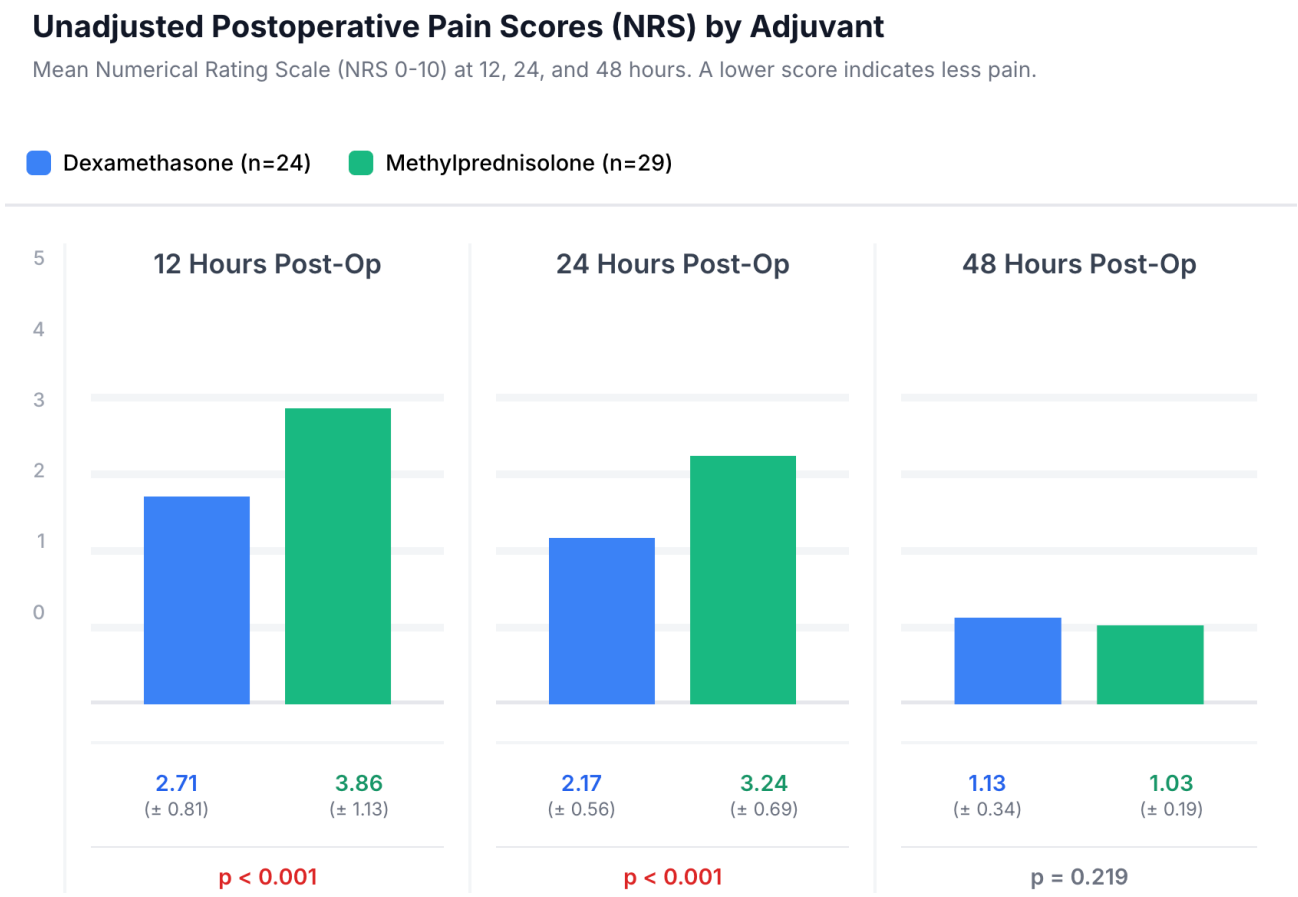

Figure 2. Comparison of unadjusted postoperative NRS pain scores.

4. Discussion

This prospective observational study was designed to explore the real-world clinical associations of two different perineural corticosteroid adjuvants—Dexamethasone Phosphate and Methylprednisolone Acetate—in adductor canal blockade for major knee surgery. The principal finding of this study, in its unadjusted analysis, is a preliminary, yet statistically significant, association between the use of perineural Dexamethasone and superior outcomes in the immediate 24-hour postoperative period: specifically, lower reported pain scores and, most critically, a higher rate of early functional mobilization.[11] Our unadjusted data show that patients in the Dexamethasone group reported mean NRS scores more than one full point lower at both 12 and 24 hours ($p < 0.001$)—a difference that is widely considered clinically significant. Congruent with this analgesic finding, the Dexamethasone group demonstrated a functionally superior outcome: 87.5% of these patients were able to successfully mobilize within 24 hours, compared to only 62.1% of the Methylprednisolone group ($p = 0.037$). By 48 hours, the analgesic differences had resolved. The central hypothesis generated by this study is that these findings are not a statistical anomaly but rather a direct clinical reflection of a pharmacodynamic mismatch.[12] We propose that the formulation of the steroid is a critical determinant of its efficacy for acute pain. The observed superiority of Dexamethasone is, we argue, the result of a rapid-acting salt (Dexamethasone Phosphate) being appropriately timed to intercept the acute inflammatory cascade, while the depot suspension (Methylprednisolone Acetate) has a pharmacokinetic profile mismatched for acute 24-hour analgesia.

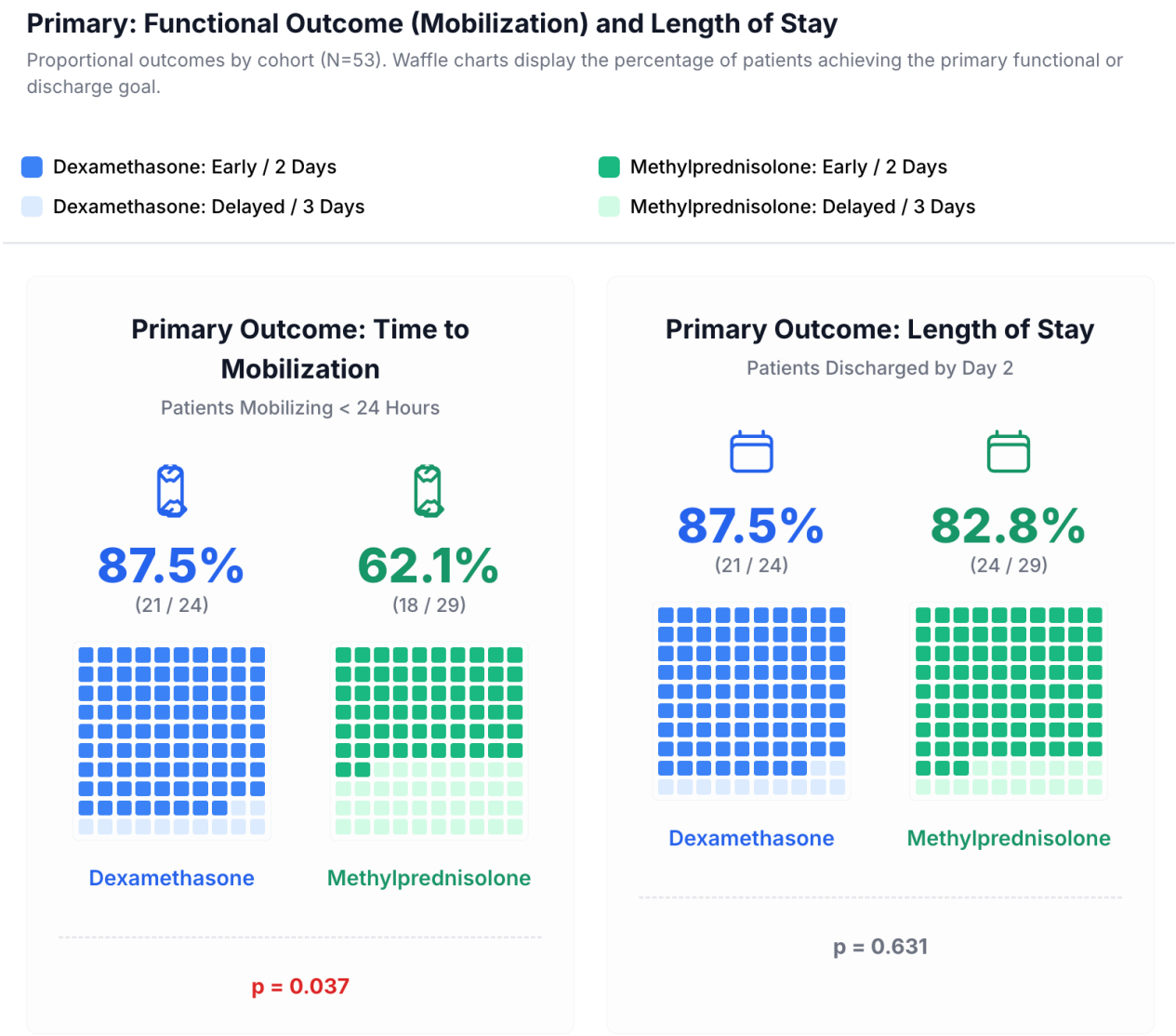

Figure 3. Primary: functional outcome (Mobilization).

To scientifically interpret our findings, one must first understand the complex, multifactorial event we are attempting to modulate: acute postoperative pain. The pain from major knee surgery, particularly TKA, is a profound physiological insult.[13] It is not a single event, but a cascade. The process begins with nociception and transduction, where the surgical incision, saw cuts through bone, and extensive soft-tissue stripping (which injures a dense network of A-delta and C-fiber nociceptors) generate a massive, synchronous volley of nociceptive signals. This is the immediate "pain signal." This initial signal, however, is not the primary driver of pain 12 hours later. The true driver of postoperative pain is the subsequent inflammatory response. Damaged cell membranes release intracellular contents (such as ATP, potassium, and protons) and activate the coagulation and complement cascades.[14] Resident mast cells degranulate, releasing histamine, serotonin, and bradykinin. The most critical step in this cascade is the activation of the enzyme Phospholipase A2, which aggressively cleaves cell membrane phospholipids to release Arachidonic Acid. This arachidonic acid is the

substrate for two key enzyme pathways: cyclooxygenase (COX-1 and COX-2) and lipoxygenase.[15] These pathways produce a local "inflammatory soup" of prostaglandins (especially PGE2), prostacyclins, leukotrienes, and thromboxanes. These eicosanoids are not, by themselves, potent pain-producers. Instead, they are powerful sensitizers. They bind to G-protein-coupled receptors (like the EP4 receptor) on the terminals of C-fiber nociceptors. This binding initiates an intracellular signaling cascade that phosphorylates and "opens" key ion channels, such as TRPV1 (the capsaicin receptor) and Nav1.8 (a tetrodotoxin-resistant sodium channel). This phosphorylation effectively lowers the activation threshold of the nerve ending. The result is peripheral sensitization: previously innocuous stimuli (like the touch of a bedsheet or gentle joint movement) are now perceived as painful (allodynia), and noxious stimuli (like bearing weight) are perceived as intensely and disproportionately painful (hyperalgesia).[16] This intense, sustained barrage of nociceptive input from the periphery rapidly overwhelms the inhibitory interneurons in the dorsal horn of the spinal cord. This leads to central sensitization (also known as "wind-up"). This process involves the glutamate-mediated expulsion of the magnesium plug from the NMDA receptor, allowing a massive influx of calcium into the dorsal horn neuron. This "wind-up" makes the spinal cord hyperexcitable, amplifying all subsequent pain signals. This combined state of peripheral and central sensitization is the pathophysiological hallmark of acute postoperative pain. It is this process, peaking between 6 and 24 hours, that must be intercepted to provide effective analgesia and permit functional recovery, in Figure 4.

Our study intervenes at the apex of this cascade using glucocorticoids, in Figure 4. Their mechanism of action is profoundly effective because it targets the source of the inflammation, not just its downstream effects (as NSAIDs do by targeting COX-2). Glucocorticoid action is multifaceted, operating on both slow genomic and rapid non-genomic pathways. The classical genomic mechanism is the primary driver of their anti-inflammatory effect. Corticosteroids are lipophilic and diffuse across the cell membrane to bind with a cytosolic Glucocorticoid Receptor (GR). This binding displaces heat-shock proteins (Hsp90, Hsp70), and the activated steroid-GR complex translocates into the nucleus. Once in the nucleus, it has two primary functions. The first, transrepression (the "brake"), is the most important anti-inflammatory action. The steroid-GR complex binds to and inhibits key pro-inflammatory transcription factors, most notably NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) and AP-1 (Activator Protein-1). By sequestering these factors, the steroid prevents them from binding to DNA and initiating the transcription of virtually all pro-inflammatory genes. This effectively shuts down the cellular factory that produces COX-2, Phospholipase A2, TNF-α, IL-1, IL-6, and various chemokines. This is a profound, top-down suppression of the entire inflammatory cascade. The second genomic function, transactivation (the "accelerator" for anti-inflammation), occurs when the complex binds directly to Glucocorticoid Response Elements (GREs) on DNA to upregulate the production of anti-inflammatory proteins. The most famous of these is Lipocortin-1 (now known as Annexin A1), which is itself a powerful direct inhibitor of Phospholipase A2, thereby cutting off the supply of arachidonic acid at its source.[17] It also upregulates IκB-α, the natural inhibitor of NF-κB, further "pressing the brake." These genomic effects, which require protein transcription and synthesis, take hours to manifest. This does not fully explain the rapid analgesic effects seen in many studies. Emerging evidence suggests that rapid, non-genomic mechanisms are also at play, particularly with high-dose steroids. These are believed to be mediated by membrane-bound GRs (mGRs) or by direct physical-chemical interactions of the steroid molecule with cellular membranes and ion channels. This rapid pathway may directly suppress ectopic neuronal firing of sensory nerves by modulating voltage-gated sodium and potassium channels, independent of inflammation. This dual-mechanism—rapid neuronal stabilization and slower, profound genomic anti-inflammation—makes perineural corticosteroids a uniquely powerful analgesic adjuvant.[18]

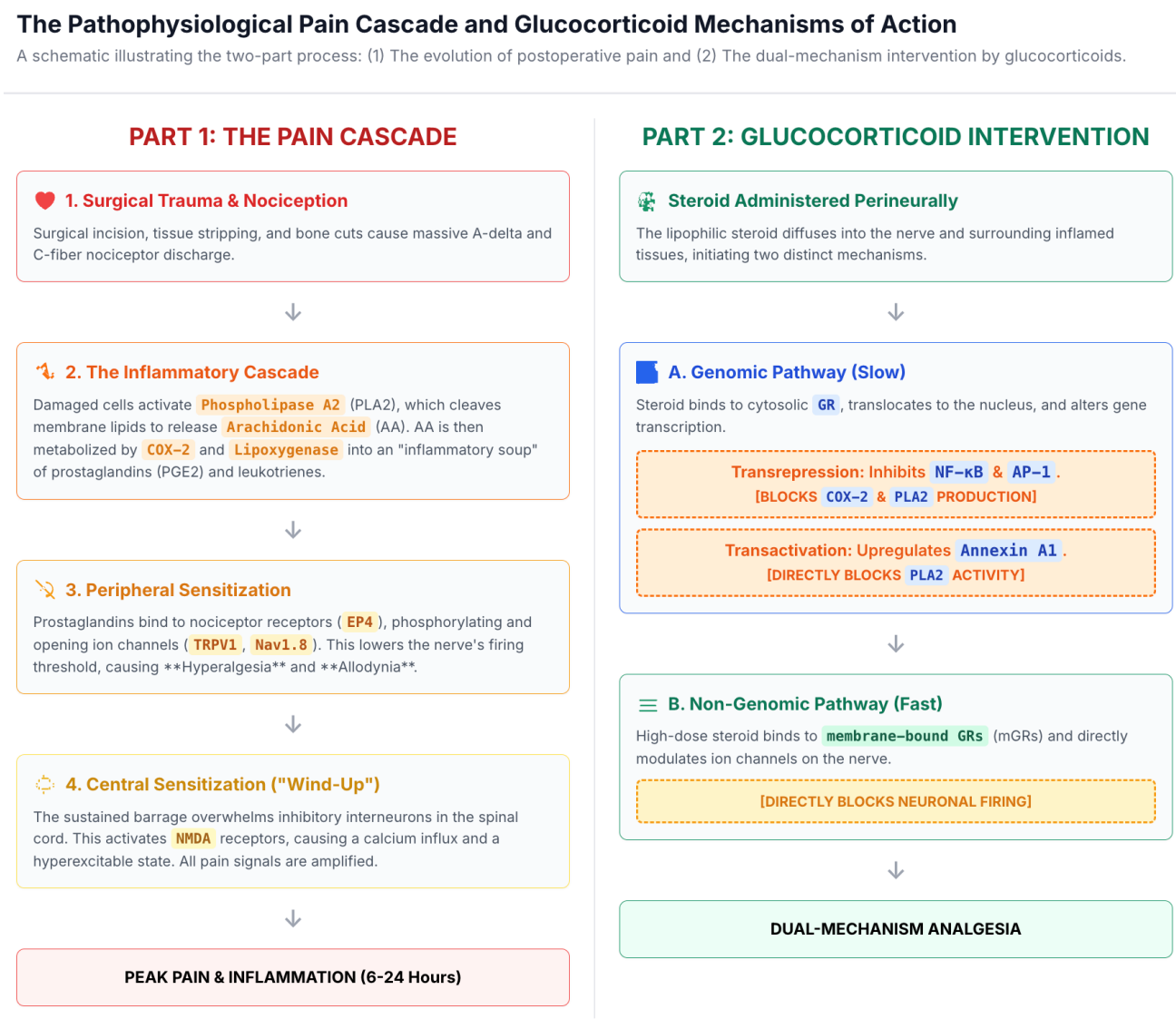

Figure 4. The pathophysiological pain cascade and glucocorticoid mechanisms of action.

This brings us to the core of our hypothesis. Our study did not simply compare two "steroids"; it compared two vastly different pharmaceutical formulations. This distinction is the most plausible explanation for our findings. We used Dexamethasone Phosphate (Group D), a highly water-soluble phosphate salt. This formulation is, upon injection, an active, unbound, and 100% bioavailable drug solution. When injected into the adductor canal, it is free to immediately diffuse into the surrounding tissues, bind to glucocorticoid receptors on local inflammatory cells, and permeate the epineurium to interact with the saphenous nerve. Its action is rapid.[19] It begins to suppress the inflammatory cascade as it is beginning. Given that the peak of surgical inflammation and peripheral sensitization occurs in the first 6-24 hours, this rapid intervention is timed perfectly to blunt this peak. This pharmacological profile—a rapid-onset, high-potency agent—provides a robust scientific rationale for our finding of significantly lower pain scores at 12 and 24 hours. Dexamethasone Phosphate is an interceptor, perfectly suited for acute pain. In stark contrast, we used Methylprednisolone Acetate (Group M). This is not a solution; it is a particulate suspension of poorly soluble acetate crystals. This formulation is a "depot" drug. It is not biologically active

upon injection. For the Methylprednisolone to work, the acetate crystals, which are phagocytosed by local tissue macrophages, must be slowly cleaved by intracellular esterases to release the free, active Methylprednisolone molecule. This process is, by design, slow and gradual, intended to provide a low-level, sustained anti-inflammatory effect over weeks (for conditions like rheumatoid arthritis), not hours. This creates a critical pharmacokinetic mismatch. In the first 12-24 hours, while the Dexamethasone Phosphate was already exerting its maximal genomic and non-genomic effects, the Methylprednisolone Acetate was likely still sitting in the adductor canal as a collection of inert crystals, having released only a fraction of its active moiety. The inflammatory cascade in Group M was allowed to proceed, relatively unchecked, for the first 12-24 hours. This provides a clear, evidence-based, pharmacological explanation for why the Methylprednisolone group reported significantly higher pain scores at 12 and 24 hours. They were, in effect, pharmacologically undertreated during this critical initial phase compared to the Dexamethasone group.[20]

Our most important finding was the statistically significant association with early mobilization ($p = 0.037$). This finding demonstrates the crucial link between effective analgesia and functional recovery, a cornerstone of ERAS. Postoperative pain is not merely an unpleasant sensory experience; it is a profound physiological inhibitor of function. Pain, especially pain with movement, triggers a cascade of neuromuscular inhibitions that form the primary barrier to mobilization. The first is Kinesiophobia, a supraspinal, fear-avoidance behavior where the patient, anticipating pain, refuses to move the limb. This is a powerful psychological component of postoperative recovery. The second is Spinal Reflex Guarding, where nociceptive input from the knee joint (transmitted by the saphenous, obturator, and genicular nerves) activates spinal reflex arcs. These arcs cause tonic, involuntary contraction (guarding) of the quadriceps and hamstring muscles, effectively "locking" the joint as a protective mechanism. The third and most significant physiological barrier is Arthrokinetic Muscle Inhibition (AMI). This is a phenomenon where pain and joint effusion (swelling)—itself an inflammatory product—are known to cause a direct, reflex-based inhibition of the cortical motor drive to the quadriceps muscle. Effusion as small as 10-20 mL can be enough to significantly impair quadriceps activation. This triad of neuromuscular inhibition is what prevents a patient from performing a straight leg raise or bearing weight. This is where the observed analgesic difference becomes critically important. At 24 hours, the Dexamethasone group reported a mean NRS of 2.17. This is well within the "mild" range, and likely below the threshold required to trigger significant neuromuscular inhibition. These patients felt comfortable enough to attempt movement. In contrast, the Methylprednisolone group reported a mean NRS of 3.24. While still "mild-to-moderate," this score was significantly higher and likely crossed the inhibitory threshold for many patients, especially during the dynamic act of mobilization (moving from sit to stand). The pain was sufficient to induce kinesiophobia and reflex guarding, leading to the observed 37.9% rate of delayed mobilization. Therefore, the observed difference in mobilization is not an independent finding; it is the direct, clinically-relevant, functional consequence of the early analgesic difference provided by the rapid-acting Dexamethasone.[17,18]

Our data show that by 48 hours, the analgesic difference between the groups had vanished ($p = 0.219$), with all patients reporting low pain scores. This is also pharmacologically plausible and provides insight into the time-course of these adjuvants. First, the natural history of acute surgical pain dictates that the initial inflammatory burst and peripheral sensitization peak within 24-48 hours and then begin to subside. The primary driver of the intense pain has diminished. Second, by 48 hours, the Methylprednisolone Acetate depot has had sufficient time to hydrolyze, and its powerful anti-inflammatory effects are likely reaching their peak, just as the single-shot bolus of Dexamethasone Phosphate is being cleared from the local tissue. The Methylprednisolone group "catches up" to the Dexamethasone group. This suggests that while Dexamethasone may be superior for the acute 0-24 hour phase, Methylprednisolone may offer a more sustained effect beyond 48 hours, though our study was not designed to detect this. This finding is critical,

as it suggests Methylprednisolone Acetate may be an inappropriate choice for acute pain, but a plausible choice for preventing delayed inflammatory pain days later. The lack of difference in Length of Stay (LOS) ($p = 0.631$) is not surprising and does not contradict the functional findings. LOS is a complex administrative and social outcome, not a direct clinical one. It is dictated by institutional discharge criteria (such as "discharge on postoperative day 2"), physiotherapy clearance, and the availability of care at home. In our hospital, a 2-day stay appears to be the standard protocol. The 25% absolute difference in 24-hour mobilization (87.5% vs 62.1%) was likely "washed out" when the remaining 37.9% of the Methylprednisolone group successfully mobilized on postoperative day 2, meeting the discharge criteria alongside everyone else.

While the pharmacological narrative is compelling and aligns perfectly with our unadjusted data, we must, as responsible scientists, acknowledge the methodological considerations that prevent us from claiming this narrative as definitive proof. Our study's strength is in its hypothesis generation, not its conclusions. First, the non-randomized, preference-based allocation is the most significant consideration. As noted in the Methods, this introduces an uncorrectable selection bias. We cannot be certain we were not simply measuring the effect of "attending preference." Our own data gives strong credence to this concern. The significant baseline difference in age distribution ($p = 0.009$) is a major confounder that directly impacts our primary functional outcome. Older age is a powerful independent predictor of delayed mobilization, separate from any analgesic regimen. It is highly plausible that the observed difference in mobilization ($p = 0.037$) is entirely, or in part, an artifact of this age difference. We did not perform a multivariate logistic regression to control for this, as we felt the number of other unmeasured confounders (BMI, baseline functional status, specific surgeon) would make such a model scientifically misleading. The finding is therefore presented as a confounded association. Second, the critical omission of rescue analgesic data renders our secondary pain score findings uninterpretable as a measure of efficacy. We can state that the Dexamethasone group reported less pain, but we cannot state their pain was better controlled, as we have no record of their rescue opioid consumption. This missing data prevents any valid multivariate analysis, such as an ANCOVA, that could have corrected for this. Finally, our dose equivalence was an approximation based on systemic effects. The true dose-response curve for perineural Dexamethasone Phosphate versus perineural Methylprednisolone Acetate is unknown. We may have been comparing a supratherapeutic dose of one agent to a sub-therapeutic dose of the other. The 10mg dose of Dexamethasone is high, and many studies suggest a "ceiling effect" for perineural analgesia at 4-8 mg. It is possible a lower, 4mg or 8mg dose of Dexamethasone would have yielded the same result with a lower risk of systemic side effects.[19,20]

This study, despite its methodological considerations, succeeds in its primary goal: it generates a powerful and testable hypothesis. The clinical implication is that not all steroids are interchangeable. The formulation (salt vs. depot) may be the most important factor in adjuvant selection for acute pain. This work provides the critical groundwork and impetus for a future definitive study. The definitive answer to this question requires a large-scale, prospective, multicenter, double-blind, randomized controlled trial. This future RCT must include: (1) Randomized Allocation to one of three arms: Ropivacaine + Dexamethasone Phosphate (8 mg), Ropivacaine + Methylprednisolone Acetate (60 mg), and a control group (Ropivacaine + saline); (2) Stratification by Age (< 65 vs. ≥ 65) and Procedure Type (TKA vs. Other); (3) A Primary Outcome of 24-hour total opioid consumption (in OME) to provide an objective measure of analgesia; (4) Secondary Outcomes including NRS scores (at rest and with movement), time to first analgesic request, time to successful mobilization, and patient-reported outcome measures (PROMs); and (5) A dedicated research team to meticulously record all rescue analgesic use. Until such a study is performed, the question of the optimal perineural corticosteroid adjuvant for adductor canal blockade remains unanswered.

5. Conclusion

This prospective observational study provides the first clinical data comparing a rapid-acting salt (Dexamethasone Phosphate) to a slow-release depot suspension (Methylprednisolone Acetate) as perineural adjuvants for adductor canal blockade. We observed strong, unadjusted associations between the Dexamethasone cohort and superior early functional recovery, as measured by 24-hour mobilization, and a superior early analgesic profile. We have proposed a compelling mechanistic rationale for these findings, centered on the pharmacodynamic mismatch between the slow-release profile of Methylprednisolone Acetate and the acute 24-hour pathophysiology of postoperative pain. However, these associations, while pharmacologically plausible, must be interpreted with extreme caution. The findings are significantly confounded by the study's observational design, non-random allocation, and a critical baseline difference in patient age. Furthermore, the lack of rescue analgesic data renders the pain score findings uninterpretable as a measure of efficacy.

6. References

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