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Postoperative Analgesic Efficacy of Dexmedetomidinein Combined with Ketamine versus Dexmedetomidine Monotherapy in Vaginal Hysterectomy under Spinal Anesthesia: Evidence-Based Review

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Abstract:

Effective postoperative pain control following vaginal hysterectomy remains essential for early mobilization, enhanced recovery, and improved overall patient outcomes. Although spinal anesthesia provides adequate intraoperative analgesia, pain commonly emerges after regression of the block, necessitating additional strategies. Dexmedetomidine, a selective α2-adrenergic agonist, offers sedative and analgesic properties without significant respiratory depression, while ketamine, an NMDA receptor antagonist, provides potent analgesia with notable opioid-sparing effects. Their combined use has attracted increasing interest within multimodal analgesia approaches. This review evaluates the postoperative analgesic efficacy of intravenous dexmedetomidine–ketamine combination compared with dexmedetomidine alone in patients undergoing vaginal hysterectomy under spinal anesthesia.

Conclusion: Available evidence suggests that adding ketamine to dexmedetomidine improves analgesic quality, prolongs pain-free duration, and reduces postoperative opioid requirements. It may also contribute to better hemodynamic balance and recovery profiles. However, heterogeneity in study designs highlights the need for further well-structured trials to define optimal dosing and safety.

Keywords: Postoperative Analgesic, Dexmedetomidine–Ketamine, Dexmedetomidine Monotherapy, Vaginal Hysterectomy

Introduction

Effective postoperative pain control remains a central component of perioperative care, particularly in gynecological procedures such as vaginal hysterectomy, where inadequate analgesia may delay mobilization, prolong hospital stay, and negatively influence overall recovery [1]. Although spinal anesthesia is widely preferred for vaginal hysterectomy due to its favorable safety profile and reduced systemic complications, it does not fully address postoperative pain once the sensory block regresses, creating a need for effective adjunctive analgesic strategies [2].

In recent years, the concept of multimodal analgesia has gained increasing attention in anesthesia and pain management practice. This approach involves combining agents with different mechanisms of action to enhance

analgesic efficacy while minimizing opioid consumption and related adverse effects [3]. Within this context, dexmedetomidine, a highly selective α2-adrenergic receptor agonist, has emerged as a valuable agent due to its sedative, anxiolytic, and analgesic properties without causing significant respiratory depression [4]. It exerts its analgesic effect through modulation of nociceptive pathways at both spinal and supraspinal levels, alongside attenuation of sympathetic activity [5].

Ketamine, on the other hand, is a well-known N-methyl-D-aspartate (NMDA) receptor antagonist that plays a key role in preventing central sensitization and reducing postoperative hyperalgesia. At subanesthetic doses, ketamine provides effective analgesia and has been shown to reduce opioid requirements in the postoperative period without significant psychomimetic effects when carefully titrated [6]. Its unique mechanism complements that of dexmedetomidine, suggesting a potential synergistic interaction when both agents are used in combination.

The combination of dexmedetomidine and ketamine has been increasingly explored as part of multimodal analgesic protocols, particularly in procedures performed under regional anesthesia. This combination may enhance analgesic depth, prolong the duration of postoperative pain relief, and improve patient satisfaction, while also stabilizing hemodynamic responses through balanced sympatholytic and sympathomimetic effects [7]. Such pharmacological synergy is of particular interest in vaginal hysterectomy, where both effective pain control and hemodynamic stability are crucial.

Despite growing clinical interest, the comparative effectiveness of intravenous dexmedetomidine–ketamine combination versus dexmedetomidine alone in this surgical setting remains an area requiring comprehensive evaluation. Variations in dosing strategies, timing of administration, and outcome measures across studies further highlight the need for an evidence-based synthesis. [7].

This review aims to critically evaluate available evidence regarding the postoperative analgesic efficacy of intravenous dexmedetomidine–ketamine combination compared with dexmedetomidine monotherapy in patients undergoing vaginal hysterectomy under spinal anesthesia, with particular focus on analgesic outcomes, opioid-sparing effects, hemodynamic stability, and recovery profiles.

Pharmacological Basis and Mechanisms of Action

A clear understanding of the pharmacological properties of dexmedetomidine and ketamine helps explain their growing role in multimodal analgesia, particularly when used together in patients undergoing procedures under spinal anesthesia. These agents act through distinct yet complementary pathways, forming the basis for their combined use in perioperative pain management strategies [8].

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist with a strong affinity for α2 receptors compared with α1 receptors. Its primary site of action is the locus coeruleus in the brainstem, where it produces sedation that resembles natural sleep. In addition, it acts at the dorsal horn of the spinal cord to inhibit the release of substance P and reduce transmission of nociceptive signals. This dual central and spinal mechanism contributes to both its sedative and analgesic effects. Unlike many sedatives, dexmedetomidine does not cause significant respiratory depression, which makes it particularly suitable in regional anesthesia settings [9].

Dexmedetomidine

Another important effect of dexmedetomidine is its sympatholytic action, which leads to reduced heart rate and blood pressure. While this may be beneficial in attenuating stress responses to surgery, excessive bradycardia or hypotension can occur, especially when used as a sole agent at higher doses. These hemodynamic effects should be carefully monitored in clinical practice, particularly in patients with limited cardiovascular reserve [10].

Ketamine, in contrast, exerts its primary effect through noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor. This receptor plays a key role in central sensitization, a process responsible for amplifying postoperative pain and contributing to hyperalgesia. By blocking NMDA receptors, ketamine reduces wind-up phenomena and prevents the development of exaggerated pain responses. At subanesthetic doses, ketamine provides effective analgesia with minimal respiratory depression [11].

Ketamine

Additionally, ketamine stimulates the sympathetic nervous system, leading to increases in heart rate and blood pressure. This property may counterbalance the hypotensive and bradycardic effects of dexmedetomidine when both drugs are administered together. However, ketamine is also associated with potential adverse effects such as hallucinations and emergence reactions, although these are less frequent at low doses and when combined with sedative agents [12].

The combination of dexmedetomidine and ketamine offers a pharmacological synergy that enhances analgesic efficacy while minimizing the limitations of each drug when used alone. Dexmedetomidine attenuates ketamine-induced psychomimetic effects, while ketamine offsets dexmedetomidine-induced bradycardia and hypotension. This complementary interaction may result in improved hemodynamic stability, prolonged analgesia, and reduced opioid consumption, making the combination particularly suitable for procedures like vaginal hysterectomy under spinal anesthesia [13].

Clinical Evidence on Postoperative Analgesia

The clinical effectiveness of dexmedetomidine in postoperative pain control has been explored in multiple surgical settings, including gynecological procedures performed under spinal anesthesia. Several studies have demonstrated that intravenous dexmedetomidine improves the quality and duration of postoperative analgesia, delays the time to first analgesic request, and reduces overall opioid consumption. These effects are attributed to its central sympatholytic and spinal antinociceptive actions. In vaginal hysterectomy, dexmedetomidine has been associated with prolonged sensory block and improved patient comfort during the early postoperative period, although its use may be limited by dose-dependent bradycardia and hypotension [14].

The addition of ketamine to dexmedetomidine has been investigated as part of multimodal analgesia strategies aiming to enhance postoperative pain control while minimizing opioid-related adverse effects. Clinical trials evaluating this combination have shown a consistent trend toward improved analgesic outcomes compared with dexmedetomidine alone. Patients receiving dexmedetomidine–ketamine combinations often exhibit lower pain scores, longer pain-free intervals, and decreased for rescue analgesics. This benefit is particularly relevant in surgeries such as vaginal hysterectomy, where moderate to severe postoperative pain is expected after regression of spinal anesthesia [15].

Dexmedetomidine-Ketamine

Evidence from randomized controlled trials in gynecological and lower abdominal surgeries supports the synergistic effect of combining dexmedetomidine with low-dose ketamine. For instance, studies have reported that this combination significantly prolongs the duration of analgesia and reduces cumulative opioid requirements within the first 24 hours postoperatively. Additionally, improved patient satisfaction scores and smoother recovery profiles have been noted. These findings highlight the clinical value of targeting multiple pain pathways simultaneously to optimize analgesic outcomes [16].

Beyond analgesic efficacy, the combination has also been evaluated for its impact on intraoperative and postoperative hemodynamic stability. Dexmedetomidine alone is known to reduce heart rate and blood pressure, whereas ketamine exerts sympathomimetic effects. When administered together, these opposing actions may result in a more balanced hemodynamic profile, reducing the incidence of clinically significant hypotension or bradycardia. This balance is particularly advantageous in patients undergoing spinal anesthesia, where sympathetic blockade already predisposes to hemodynamic fluctuations [17].

However, despite these promising findings, heterogeneity remains among studies in terms of dosing regimens, timing of administration, and outcome measures. Some variability also exists regarding the incidence of adverse effects, including sedation levels and emergence phenomena. While low-dose ketamine generally does not increase psychomimetic complications when combined with dexmedetomidine, careful titration and monitoring remain essential. Therefore, although current evidence supports the superiority of the combination over monotherapy in many aspects, further well-designed, procedure-specific trials are needed to establish standardized protocols [18].

Opioid-Sparing Effects and Impact on Recovery Profile

Opioid-sparing analgesia has become a major target in contemporary perioperative care because reducing postoperative opioid exposure may lower the risk of nausea, vomiting, ileus, sedation, delayed ambulation, and prolonged hospitalization. In gynecologic surgery, ERAS recommendations specifically support multimodal, opioid-sparing strategies to improve recovery and patient comfort, which makes the evaluation of dexmedetomidine and ketamine especially relevant in vaginal hysterectomy performed under spinal anesthesia [19].

Dexmedetomidine has shown a meaningful opioid-sparing effect across surgical populations. A recent Bayesian meta-analysis reported that intraoperative dexmedetomidine likely improves postoperative quality of recovery and can reduce pain burden, although this benefit should be balanced against a higher likelihood of bradycardia and hypotension. These findings support its role as a valuable adjunct when the goal is to decrease postoperative analgesic requirements without causing respiratory depression [20].

From a recovery perspective, dexmedetomidine may also improve early postoperative comfort beyond pain scores alone. In a randomized controlled trial in breast surgery, a single intraoperative dose improved quality-of-recovery measures, reduced analgesic requirements, and lowered the incidence of postoperative nausea and vomiting in the early postoperative period. Although this study was not conducted in vaginal hysterectomy, it supports the concept that dexmedetomidine can positively influence clinically relevant recovery endpoints that matter to patients after surgery [21].

Ketamine also contributes to opioid-sparing analgesia through NMDA receptor antagonism and prevention of central sensitization. Consensus guidance on intravenous ketamine for acute pain supports its perioperative use, particularly when opioid minimization is desirable. More recently, a 2024 meta-analysis found that perioperative ketamine or esketamine was associated with improved early subjective quality of recovery, lower pain severity, and fewer psychological symptoms after surgery without a clear increase in overall adverse events. These findings strengthen the rationale for adding low-dose ketamine to dexmedetomidine rather than relying on dexmedetomidine monotherapy alone [22,23].

When both agents are combined, the expected clinical advantage is not simply lower pain scores, but a broader recovery benefit driven by reduced rescue analgesic use, less opioid exposure, smoother emergence, and better tolerance of the early postoperative phase. Comparative clinical work has shown that low-dose ketamine and dexmedetomidine each can reduce postoperative analgesic requirements with limited adverse effects, while multimodal use is pharmacologically attractive because dexmedetomidine can blunt ketamine-related psychomimetic reactions and ketamine may offset excessive sympatholysis from dexmedetomidine. For patients undergoing vaginal hysterectomy under spinal anesthesia, this combination may therefore support a more balanced recovery profile, though procedure-specific trials remain necessary to define the optimal regimen and confirm the magnitude of benefit [22-24].

Hemodynamic Effects, Sedation Profile, and Safety Considerations

Hemodynamic control is especially important in vaginal hysterectomy performed under spinal anesthesia because neuraxial sympathetic blockade already predisposes patients to hypotension and bradycardia. In this setting, the choice of intravenous adjuvant can influence not only analgesic quality but also cardiovascular stability during the intraoperative and early postoperative periods. Dexmedetomidine is well known for its sympatholytic effect, which can be clinically useful in blunting stress responses, yet this same property may increase the risk of bradycardia and hypotension, particularly when a loading dose or higher infusion rates are used [25,26].

From the sedation standpoint, dexmedetomidine offers a distinct advantage because it provides cooperative sedation with little clinically relevant respiratory depression. This makes it attractive during regional anesthesia, where maintenance of spontaneous ventilation and easy patient arousability are desirable. However, although respiratory compromise is less common than with many conventional sedatives, careful monitoring remains necessary, especially in elderly patients, those with cardiovascular disease, and those receiving additional sedative or analgesic medications [27].

Ketamine has a different hemodynamic profile. At analgesic or subanesthetic doses, it tends to preserve airway reflexes and respiratory drive while producing sympathetic stimulation that may increase heart rate and blood pressure. This effect can be helpful when spinal anesthesia or dexmedetomidine causes excessive sympathetic depression. At the same time, ketamine is associated with dose-dependent adverse effects, particularly dysphoria, hallucinations, and other psychomimetic symptoms, although these are less frequent with low-dose perioperative use [22,28].

The rationale for combining dexmedetomidine with ketamine is that each drug may offset part of the other's limitations. Dexmedetomidine can reduce ketamine-related agitation and emergence reactions, whereas ketamine may lessen excessive decreases in heart rate and blood pressure caused by dexmedetomidine. Clinical reports and comparative studies in procedural sedation and regional anesthesia have described better hemodynamic balance and acceptable sedation conditions with the combination than with either agent alone in some settings, which supports its relevance for vaginal hysterectomy under spinal anesthesia [13,29].

Safety still depends on dose selection, timing, and patient characteristics. Available evidence suggests that the combination is generally well tolerated when low-dose ketamine is paired with carefully titrated dexmedetomidine, but clinicians should continue to watch for bradycardia, hypotension, oversedation, nausea, and occasional neuropsychiatric symptoms. In practice, the combined regimen appears most attractive when the aim is to achieve adequate analgesia and sedation without heavy opioid exposure, while maintaining a more stable perioperative course than dexmedetomidine monotherapy may provide in vulnerable patients under spinal anesthesia [20,22,30].

Limitations of Current Evidence and Future Research Directions

Although the available literature supports the analgesic and opioid-sparing value of dexmedetomidine and low-dose ketamine, the current evidence base for their direct comparison in vaginal hysterectomy under spinal anesthesia remains limited. Much of the published work comes from heterogeneous surgical populations, including lower abdominal surgery, breast surgery, orthopedic procedures, and procedural sedation studies, rather than from procedure-specific trials focused on vaginal hysterectomy. This limits the strength of direct clinical inference for the exact population addressed in this review [20,23,28].

Another important limitation is the wide variation in study methodology. Published studies differ in dexmedetomidine loading dose, maintenance infusion rate, ketamine dose, timing of administration, use of additional analgesics, and the primary outcomes selected for analysis. Some trials focus mainly on pain scores, whereas others prioritize rescue analgesic requirement, time to first analgesic request, sedation level, or hemodynamic changes. This methodological inconsistency makes pooled interpretation difficult and reduces the ability to define an optimal regimen for clinical practice [20,22,23].

The assessment of recovery also remains incomplete in many studies. While pain scores and opioid consumption are commonly reported, patient-centered endpoints such as early mobilization, readiness for discharge, postoperative nausea and vomiting, sleep quality, functional recovery, and overall quality-of-recovery scores are less consistently measured. This is important because the clinical value of combining dexmedetomidine with ketamine should not be judged by analgesia alone, but by its ability to improve the full postoperative course after vaginal hysterectomy [19,20,23].

Safety data also need more precise characterization. Dexmedetomidine is associated with bradycardia and hypotension, while ketamine may cause neuropsychiatric adverse effects, tachycardia, or increased secretions, depending on dose and context. Although combination therapy may theoretically balance some of these effects, existing studies are often underpowered to detect uncommon but clinically relevant adverse events, especially in older patients and those with cardiovascular comorbidity. More robust safety-focused trials are needed before firm conclusions can be made about the superiority of one regimen over another [22,25,28].

A further point is that the direct clinical question addressed in this review is still emerging in formal trial registration. A recent registered study specifically examining intravenous dexmedetomidine–ketamine versus dexmedetomidine alone for postoperative analgesia in vaginal hysterectomy under spinal anesthesia indicates active interest in this topic, but it also highlights that published high-quality evidence remains limited at present.

Until more results become available, current conclusions must remain cautious and based partly on extrapolation from related perioperative settings [31].

Future research should focus on well-designed randomized controlled trials in vaginal hysterectomy patients under standardized spinal anesthesia protocols. These trials should compare clearly defined dosing schedules, include adequate sample sizes, and assess not only pain intensity and analgesic consumption but also recovery quality, patient satisfaction, functional outcomes, hemodynamic stability, and adverse-event profiles. Such work would help determine whether the dexmedetomidine–ketamine combination offers a truly meaningful clinical advantage over dexmedetomidine monotherapy and would support the development of practical perioperative protocols for gynecologic anesthesia [19,20,22].

Conclusion

The available evidence indicates that intravenous dexmedetomidine provides effective postoperative analgesia with a clear opioid-sparing benefit in patients undergoing surgery under spinal anesthesia, including vaginal hysterectomy. However, the addition of low-dose ketamine appears to further enhance analgesic efficacy by targeting complementary pain pathways, leading to prolonged pain-free intervals, reduced need for rescue analgesia, and potentially improved early recovery profiles. This multimodal approach aligns well with current perioperative strategies aimed at minimizing opioid exposure while maintaining effective pain control.

At the same time, the dexmedetomidine–ketamine combination offers a more balanced hemodynamic and sedation profile compared with dexmedetomidine alone, although careful dosing and monitoring remain essential to avoid adverse effects. Despite promising findings, the current evidence is still limited by heterogeneity and a lack of procedure-specific high-quality trials. Future well-designed randomized studies in vaginal hysterectomy are needed to establish standardized protocols and confirm the clinical superiority and safety of this combination in routine anesthetic practice.

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