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Efficacy and duration of analgesia with levobupivacaine combined with fentanyl or dexmedetomidine in lower extremity surgery: A meta-analysis

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ABSTRACT

Background: In combination with local anesthetics such as levobupivacaine, fentanyl, and dexmedetomidine improve post-operative analgesia after surgery on the lower extremities. **Aims and Objectives:** To determine whether the local anesthetic levobupivacaine in combination with fentanyl or dexmedetomidine can improve the efficacy and duration of analgesia in lower extremity surgery. **Materials and Methods:** After a search in PubMed, Google, and Web of Science, six randomized controlled trials with 400 patients were found. Review Manager 5 was then used to retrieve the study results and calculate the effect sizes. **Results:** The effects of 0.5% levobupivacaine with fentanyl (group F) and dexmedetomidine (group D) on sensory blockade, regression, and post-operative analgesia were investigated in numerous studies. Group D had a significant advantage in sensory regression (standard mean difference [SMD] −3.34, confidence interval [CI] [−4.07, −2.62], P<0.00001), although there was no significant difference in the onset of sensory blockade (SMD −0.21, CI [−1.28, 0.86], dexmedetomidine prolonged post-operative analgesia (SMD −7.34, CI [−11.08, −3.60], P=0.0001). The heterogeneity between the studies was substantial (I^2=59–97%). The methodological excellence of the selected studies was reflected in their low risk of bias in all areas. **Conclusion:** Despite the identical onset of sensory blockade, dexmedetomidine prolongs sensory regression and post-operative analgesia more than fentanyl. Despite considerable variability, these results are supported by a low bias, making dexmedetomidine a better adjuvant for analgesia in chronic lower extremity surgery.

Key words: Spinal block; Post-operative pain; Adjuvant; Sensory block; Motor block

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INTRODUCTION

General anesthesia and regional anesthesia are frequently used for lower limb surgery. Regional anesthesia – including limb, trunk, and plexus blocks – reduces post-operative pain, speeds recovery, and reduces systemic problems. Epidural and spinal anesthesia, which are major modes of central neuraxial anesthesia, are commonly used in regional anesthesia for lower limb surgery. It is important to differentiate between these approaches and use accurate terminology as each approach has different therapeutic applications and benefits depending on the surgery and patient.

These advantages include maintaining patient consciousness, providing adequate analgesia, reducing stress, reducing

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intraoperative bleeding, minimizing post-operative pain, allowing earlier mobilization, and improving rehabilitation.[1]

Bupivacaine is a local anesthetic that has been used for more than 40 years; it contains long-acting amide groups. This chemical has been associated with a number of adverse effects since its introduction in 1957, including cardiovascular and central nervous system toxicity. This motivated research to develop a more modern and safer local anesthetic.[2]

Levobupivacaine is a stereoisomer of bupivacaine, an amide local anesthetic, with similar properties to bupivacaine in terms of duration, quality, and onset of sensory blockade, but with fewer neurotoxic and cardiac side effects. Its safety and efficacy in local anesthetic procedures with mild hemodynamic changes have been clinically proven. Due to its low lipid solubility, which blocks sensory nerve fibers more than motor fibers, it allows for better sensory-motor discrimination. A lower risk of venous thromboembolism is associated with early recovery of motor function.[3,4]

In addition, levobupivacaine causes earlier recovery of motor blockade compared to bupivacaine. Adjuvants can be administered simultaneously to reduce the toxicity of local anesthetics and improve the efficacy of perineural blocks. Adjuvants include fentanyl and other opioids, which have a strong anesthetic effect in combination with local anesthetics.[5]

Nowadays, newer phenylpiperidine drugs such as fentanyl and sufentanil are often used for segmental analgesia. As they are more lipid soluble and have a higher affinity for opioid receptors, these drugs provide a faster onset of the blockade, improve the quality of intraoperative anesthesia, and prolong post-operative analgesia with fewer side effects.[6]

Fentanyl is the most commonly used short-acting opioid in combination with intrathecally administered local anesthetics. It interacts with local anesthetics and improves the quality of both intraoperative and post-operative analgesia.[7] When fentanyl is injected intrathecally at a dose of 10–25 mg, post-operative analgesia has been reported to last up to 180–240 min.[5] However, intrathecal opioids can have a number of negative side effects, such as urinary retention, nausea, vomiting, pruritus, and respiratory depression.[7,8]

Dexmedetomidine, a new selective α2-agonist, is currently being introduced as a sedative, sympatholytic, and analgesic adjuvant to local anesthetics.[8-10]

It acts on pre- and post-synaptic nerve endings and on the central nervous system to reduce sympathetic outflow and noradrenaline release. This leads to hemodynamic, analgesic, sympatholytic, sedative, and anxiolytic properties.[11-13] There are no opioid-related side effects such as respiratory depression, nausea, or vomiting, while bradycardia and hypotension. Side effects of dexmedetomidine-induced motor blockade.[13] Numerous studies have shown that intraurethral dexmedetomidine injection prolongs analgesia and attenuates the negative effects of opioid administration.[8-10,14] However, recent research suggests that intrathecal dexmedetomidine injection is often associated with certain side effects, such as a decrease in heart rate and blood pressure.[15-18] In this meta-analysis, we tried to evaluate the efficacy and safety of fentanyl and dexmedetomidine as adjuvants to intrathecal levobupivacaine in lower extremity surgery.

Aims and objectives

To evaluate the efficacy and safety of fentanyl and dexmedetomidine as adjuvants to intrathecal levobupivacaine in lower extremity surgery.

MATERIALS AND METHODS

This meta-analysis study was conducted in the Department of Anesthesiology and Critical Care, Gautam Buddha Chikitsa Mahavidyalaya, Dr KKBM Subharti Hospital, Dehradun.

Identification and procedure: Literature search and study selection

The researchers independently searched PubMed, Google, and Web of Science for articles on fentanyl and dexmedetomidine as adjuvants to intrathecal levobupivacaine for lower extremity surgery. The following search terms were used: (onset of sensory OR motor blockade) AND (duration of motor blockade OR duration of analgesia) AND (lower limb surgery OR lower extremity surgery OR local anesthetic OR levobupivacaine OR adjuvant OR fentanyl OR dexmedetomidine). In addition, a manual search of all articles and journal references was performed to find further relevant studies.

Results were limited to lower extremity surgery, levobupivacaine-based local anesthetics, adjuvants such as fentanyl and dexmedetomidine, timing of sensory and motor blockade, duration of motor blockade, and duration of analgesia. The search results from PubMed, Google, and Web of Science yielded a total of 178 articles.

Inclusion criteria

Randomized controlled trials, Studies comparing 0.5% levobupivacaine with dexmedetomidine versus 0.5% levobupivacaine with fentanyl, published articles, Full articles available in English.

Exclusion criteria

Studies conducted on animals.

The primary consideration for study selection was to evaluate the duration of post-operative analgesia, onset, duration of sensory and motor blockade, and adverse effects associated with the addition of fentanyl and dexmedetomidine as adjuvants to hyperbaric 0.5% levobupivacaine in lower extremity surgery.

Data collection

For each study, data were retrieved from the text, photographs, or tables covering targeted objectives such as duration of surgical analgesia, onset and duration of sensory and motor blockade, and side effects. Studies comparing 0.5% levobupivacaine with the addition of fentanyl (group F) versus dexmedetomidine (group D) were included. Preplanned assumptions and simplifications were considered during data extraction. After excluding high-risk studies, sensitivity analyses were performed for each included study. For the synthesis, effect measures were defined for each outcome (Figure 1).

Synthesis of the data

The following data were collected for each study: Article title, lead author name, journal name, date of publication, nation name, and block type.

Statistical analysis

Review Manager 5.3 (RevMan 5.3) from the Cochrane Collaboration based in London, United Kingdom, was used for statistical analysis. The time intervals between motor blockade, onset of sensory and motor blockade, and analgesia were measured using the mean difference and its 95% confidence interval (CI). The I2 statistic and Q(2) test were used to assess the heterogeneity of the study. We calculated the effect size using the random effects model assuming significant heterogeneity. In addition, a sensitivity analysis was performed to investigate the causes of heterogeneity. For the effect sizes, a P=0.05 was considered statistically significant.

RESULTS

Search results

Figure 1 shows the flow diagram of the search, screening, eligibility, and selection process for published articles included in this meta-analysis. Initially, a total of 205 published articles were retrieved. After removing 15 duplicate articles, 188 references were reviewed for relevance. Based on titles and abstracts, 173 articles were excluded due to irrelevant data. After reviewing abstracts, nine more articles were excluded. A total of 20 articles were selected for full-text review. However, many studies were excluded at this stage due to insufficient data or because they were conference papers. The final set of

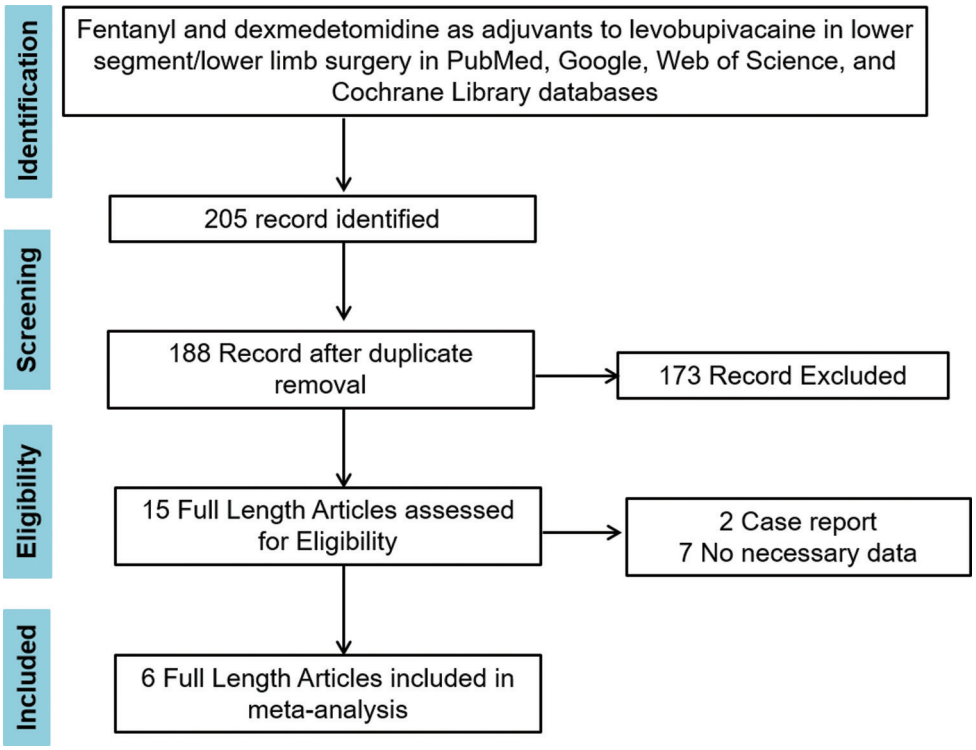

Figure 1: Article searching, screening, eligibility, and included or selection process

studies included in the meta-analysis was determined from this thorough screening process. A total of six studies were included in the meta-analysis, comprising 208 patients who received 0.5% levobupivacaine with dexmedetomidine (group D) and 208 patients who received 0.5% levobupivacaine with fentanyl (group F). Six publications[19-24] were finally considered for the meta-analysis, which focused on the onset of sensory and motor blockade, the interval of motor blockade, and the interval of analgesia (Table 1 and Figure 1).

Onset of sensory block

The assessment of the onset of sensory blockade was performed in six studies, involving 200 participants in the 0.5% levobupivacaine with fentanyl group (group F) and 200 participants in the 0.5% levobupivacaine with dexmedetomidine group (group D). The onset of sensory block after lower extremity surgery was recorded for both groups during each examination. There was significant heterogeneity between the studies ($P<0.00001$, $I^2=96\%$). The onset of sensory blockade varied considerably in the studies. Overall, no statistically significant difference was found between the groups (standard mean difference [SMD]: −0.21; 95% CI: [−1.28, 0.86]; P=0.70). The risk of bias in all studies was consistently low, reflecting reliable randomization, blinding, and outcome reporting. However, the significant heterogeneity suggests variability in research methodologies or participant demographics, requiring careful interpretation of the findings (Figure 2).

Onset of motor block

The onset of motor blockade was investigated in six studies involving 200 patients receiving 0.5% levobupivacaine with fentanyl (group F) and 200 patients receiving 0.5% levobupivacaine with dexmedetomidine (group D). For group F and group D, the onset of motor block after lower extremity surgery was recorded at each examination. There was significant heterogeneity between studies ($P<0.00001$, $I^2=96\%$). The onset of motor block varied significantly across studies. The overall effect was no significant difference found between groups (SMD 0.16, CI (−0.94–1.26), P=0.77). The risk of bias assessment showed a low risk of bias for each study in all categories, confirming the methodological quality of the included studies. Although the risk of bias is minimal, the significant heterogeneity found indicates different research methods, which must be taken into account when interpreting the results (Figure 3).

Time to two-segment sensory regression

Assessment of the time to two-segment sensory regression was performed in three studies, including 90 (0.5%) levobupivacaine with fentanyl in group F and 90 (0.5%) levobupivacaine with dexmedetomidine in group D. For group F and group D, the time to two-segment sensory regression after lower extremity surgery was recorded at

Table 1: Characteristics/information of the studies included in the meta-analysis

Studies	Surgery	Measures	Groups (n): treatment
Jain et al.,[19]	Infraumbilical surgeries	Onset and duration of sensory and motor block, duration of post-operative analgesia, and side effects	Group D: received 12.5 mg hyperbaric levobupivacaine + 5 μg dexmedetomidine Group F: received 12.5 mg hyperbaric levobupivacaine + 25 μg fentanyl
Mahilamani and Johnet,[20]	Lower limb orthopedic surgery	Sensory and motor block, Duration of analgesia, Side effects	Group D: Received 14 mL 0.5%levobupivacaine with 25 mcg dexmedetomidine Group F: Received 14 mL 0.5% levobupivacaine with 50 mcg Fentanyl
Chandra et. al.,[21]	Lower limb surgeries	Onset and duration of sensory and motor block, duration of post-operative analgesia, and side effects	Group D: received 0.5% Levobupivacaine 12 mg + 10 mcg Dexmedetomidine Group F: Received 0.5% Levobupivacaine 12 mg + Fentanyl 25 mcg,
Bhure and Jagtap,[22]	Lower limb orthopedic surgery	Onset and duration of sensory block, maximum sensory block. Onset and duration of motor block, maximum motor block, time to regress sensory, and motor block, post-operative analgesia. Level of sedation, hemodynamic changes, side effects.	Group D: 0.5% isobaric levobupivacaine 3 mL + 5 mcg dexmedetomidine diluted with NS=3.5 mL Group F: 0.5% isobaric levobupivacaine 3 mL + 25 mcg fentanyl diluted with NS=3.5 mL.
Zafar et al.,[23]	Lower segment cesarean section	Sensory and motor block, Duration of analgesia, Side effects	Group D: received 2.5 mL isobaric levobupivacaine and 5 μg dexmedetomidine, Group F: received 2.5 mL isobaric levobupivacaine and 25 μg fentanyl
Shukla et al.,[24]	Lower limb orthopedic surgeries	Sensory and motor block, Two segment regression and regression of motor block to Bromage score 2, Duration of analgesia, Side effects	Group D received 15 mL of 0.5% levobupivacaine and 25 μg in 2 mL of dexmedetomidine, Group F received 15 mL of 0.5% levobupivacaine and 50 μg in 2 mL of fentanyl

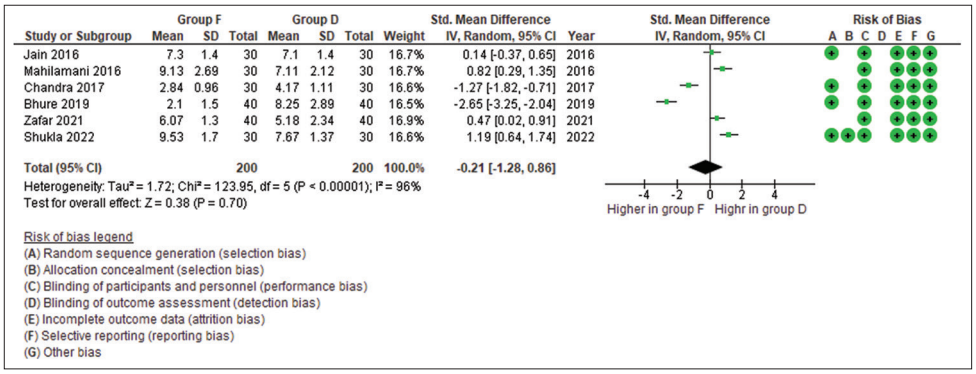

Figure 2: Forest plots of association of onset of sensory block between group F and group D in lower extremity surgery

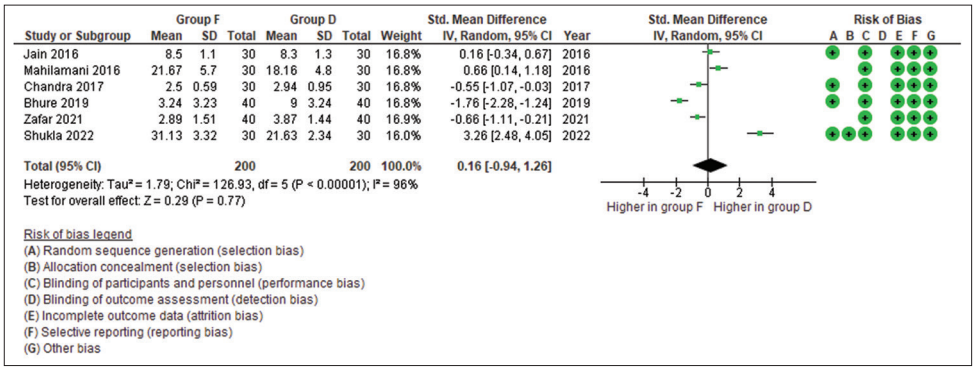

Figure 3: Forest plots of association of onset of motor block between group F and group D in lower extremity surgery

each examination. There was no significant heterogeneity between the studies (P=0.09, I²=59%). The time to sensory regression in two segments did not vary significantly between the studies. However, a significant overall difference was observed between the groups (SMD: −3.34; 95% CI: [−4.07–−2.62]; P<0.001). The assessment of the risk of bias showed a minimal risk in all areas, which speaks for a high methodological quality. The data show that dexmedetomidine significantly prolongs the duration of sensory blockade compared to fentanyl (Figure 4).

Duration of analgesia

The duration of analgesia was investigated in four studies involving 130 patients receiving 0.5% levobupivacaine with fentanyl (group F) and 130 patients receiving 0.5% levobupivacaine with dexmedetomidine (group D). For both groups, the duration of analgesia after lower extremity surgery was recorded at each evaluation. There was significant heterogeneity between studies (P<0.00001, I2=97%). The duration of analgesia varied significantly across studies. The overall effect was a significant difference found between groups (SMD −7.34, CI (−11.08–−3.60), P<0.001). The risk of bias assessment was minimal in all areas, confirming the integrity of the results. The results show that dexmedetomidine provides significantly longer post-operative analgesia compared to fentanyl (Figure 5).

DISCUSSION

Meta-analysis is an effective analytical tool for compiling data from studies with low power. This meta-analysis demonstrates that while the addition of fentanyl or dexmedetomidine to a local anesthetic in lower extremity surgery does not significantly affect the onset time of sensory and motor blockade, dexmedetomidine provides a notable advantage by prolonging the time to two-segment sensory regression and extending the duration of postoperative analgesia.

The primary outcome of this meta-analysis was the post-operative duration of analgesia. The duration of analgesia is considered the gold standard for evaluating the efficacy of a drug. This enhancement may be attributed to the synergistic interaction between dexmedetomidine and levobupivacaine, whereby dexmedetomidine enhances the local anesthetic efficacy of levobupivacaine by enhancing hyperpolarization-activated cation currents and impeding the transmission of pain signals, resulting in prolonged and more potent analgesia.

The meta-analysis showed that the duration of analgesia was significantly longer in the group that received anesthesia with dexmedetomidine after surgery. Second, the

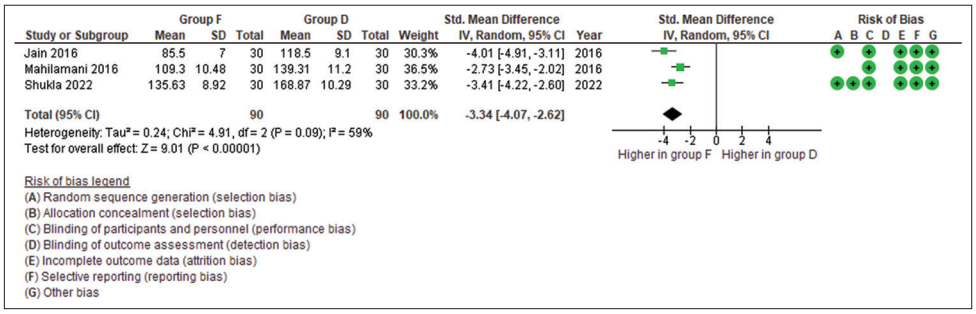

Figure 4: Forest plots of association of time to two-segment sensory regression between group F and group D in lower extremity surgery

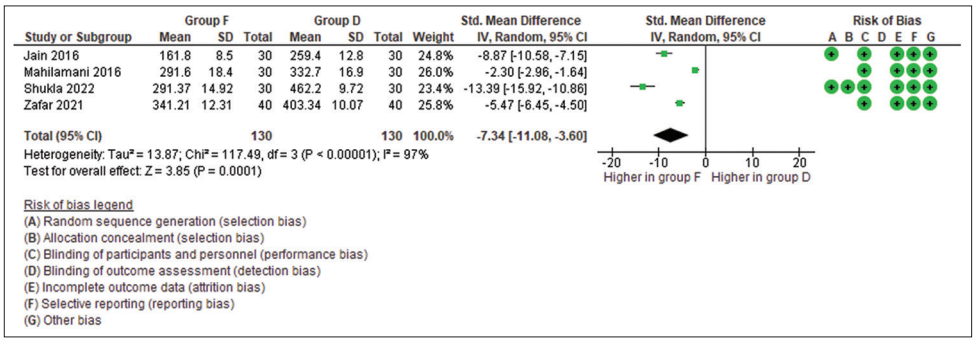

Figure 5: Forest plots of association of duration of analgesia between group F and group D in lower extremity surgery

time to regression of the two-segment sensory blockade was significantly prolonged in the dexmedetomidine group, whereas the duration of onset of sensory and motor blockade did not differ significantly between the fentanyl and dexmedetomidine groups.

It is well known that post-operative pain is often not adequately treated. A short period of analgesia after surgery is associated with the routine use of local anesthetics in lower extremity procedures. Levobupivacaine is a local anesthetic that is slower-acting than bupivacaine and has a higher safety margin. Its pharmacological structure is identical to that of bupivacaine. Compared to bupivacaine, levobupivacaine has less inotropic effects and prolongs the QTc interval less, and its depressive effect on QRS duration and AV conduction is less. In elective hip surgery compared levobupivacaine with racemic bupivacaine and showed that levobupivacaine is less neurotoxic and cardiotoxic.[25]

We compared the effects of adding different adjuvants to levobupivacaine, as there are not many studies on this drug. Fentanyl has been used as an intrathecal adjuvant for many years. Fentanyl is a lipophilic, μ-receptor agonist opioid that acts rapidly. It has been administered intrathecally as an adjuvant for more than 20 years.[26,27] The substantia gelatinosa in the spinal cord contains the largest concentration of μ-receptors. Direct administration of fentanyl to these receptors inhibits the presynaptic release of substance P in primary sensory neurons, resulting in profound analgesia. This is caused by a decrease in intracellular cyclic adenosine monophosphate associated with an increase in K+ influx and inhibition of G-protein mediated Ca2+ influx. This leads to a decrease in synaptic transmission, hyperpolarization of neuronal membranes, and a decrease in neurotransmitter release.[28] With an a2/a1 binding affinity ratio of 1620:1, dexmedetomidine is a novel, highly selective a2 agonist that exhibits 8 times better selectivity for a2 receptors than clonidine.[19]

According to Shukla et al.,[24] sensory blockade at the T10 level was slowest in the levobupivacaine group, whereas it was fastest in the dexmedetomidine group (P<0.001), followed by the fentanyl and tramadol groups. In a prospective, randomized, double-blind clinical trial, early sensory blockade up to the T10 level occurred in the dexmedetomidine group.[29] Similarly, another study found that levobupivacaine plus dexmedetomidine caused early sensory blockade at the T10 level (P=0.036)[20]

Esmaoğlu et al.,[30] found in their study that intrathecal administration of 3 μg dexmedetomidine in combination with levobupivacaine during spinal anesthesia shortened the duration of blockade and prolonged the time of onset of blockade for both motor and sensory blockades without causing significant side effects. However, Jain et al.,[19] found no statistically significant difference between the onset times of sensory and motor blocks between dexmedetomidine and fentanyl groups. According to Pathak and Krishna,[31] dexmedetomidine participants on average achieved complete motor blockade in significantly less time (P<0.001) than

fentanyl patients, suggesting that the onset of motor blockade was faster in dexmedetomidine participants. Compared to the levobupivacaine with fentanyl group and the levobupivacaine with dexmedetomidine group (5.18±2.34 min, 6.07±5.13 min), the maximum time for sensory block was 8.09±2.11 min for levobupivacaine in the study by Zafar et al.[23] They also found that the mean scores of the three groups on Bromage scale 3 were statistically significantly (P<0.003) lower than for fentanyl (2.89±1.51). Similar results were also obtained in an earlier study.[32] In group II, the maximum time required for sensory regression to level S1 (sensory block length) was 501.04±14.34 min, which was high among the three groups (P<003). Dexmedetomidine, particularly at a 3μg dose, enhances intraoperative somato-visceral sensory blockade.[33] According to Bhure et al.,[22] the mean time to onset of sensory block was 10.70±3.93 min in the saline group, 8.25±2.89 min in the dexmedetomidine group, and 2.10±1.15 min in the fentanyl group. The sensory block therefore started earlier in the fentanyl group. According to one study, the onset of sensory blockade was significantly faster in the dexmedetomidine group (3.90±0.94 min) than in the fentanyl group (3.22±0.69 min).[34] According to another study, the lipophilic properties of fentanyl explain its early onset.[35] The lipophilic opioids rapidly penetrate the dura mater, where they are trapped in the epidural fat and eventually enter the systemic circulation. They also rapidly pass through the spinal cord, where they bind to opioid receptors in the dorsal horn and white matter before being released from the spinal cord and entering the systemic circulation. In a previous study,[36] sensory blockades were shown to occur up to the T10 level. It was 7.4±3.3 min in the fentanyl group and 7.5±7.4 min in the dexmedetomidine group.

According to Shukla et al., the dexmedetomidine group had the longest mean time to two-segment regression of sensory blockage. Jain et al., Mahilamani and John and Jain et al., demonstrated that there was a significant difference in two-segment regression of sensory blockade between fentanyl and levobupivacaine when dexmedetomidine was used. In addition, another study found that dexmedetomidine prolonged the duration of two-segment regression.[37] A previous study found that the dexmedetomidine group had a longer two-segment recovery time (P=0.001) than the levobupivacaine group.[38]

According to previous studies, the mean duration of analgesia peaked with dexmedetomidine and with fentanyl used as an adjuvant to levobupivacaine. According to another study, analgesia lasted longer in subjects receiving levobupivacaine with dexmedetomidine than in subjects receiving levobupivacaine with fentanyl.[31] Shukla et al., showed that the group that also received dexmedetomidine had a lower total VAS score than the other groups. Similarly, the study by Paul et al.[37] showed a decrease in post-operative VAS score at 12, 18, and 24 h in the dexmedetomidine control group compared to the fentanyl group. In another study, patients undergoing major abdominal cancer surgery reported greater pain relief (lower VAS score) in the dexmedetomidine group.[39] Compared to the fentanyl group, the dexmedetomidine group required less diclofenac.[24] Previous studies reported that the incidence of side effects such as nausea, vomiting, shivering, and urinary retention were not significantly different in fentanyl and dexmedetomidine groups.[18-24]

When interpreting the results, the numerous limitations of the meta-analysis should be taken into account. In addition, several limitations must be considered when interpreting our results. First, our results may be biased by small study effects, as this meta-analysis included only six studies, each with a sample size of <41 patients. The included studies differed in the type and amount of local anesthetics used and in the dosage of fentanyl and dexmedetomidine. This could potentially affect the validity of the pooling effects. Second, the included studies show some clinical heterogeneity. Third, although the use of adjuvants in combination with local anesthetics is currently a popular topic, due to the small number of included studies, further research is needed to decide whether fentanyl or dexmedetomidine is the best adjuvant.

RESULTS

Dexmedetomidine, when added to levobupivacaine, significantly prolonged the time to regression of the two-segment sensory response and the duration of postoperative analgesia compared with fentanyl, but the onset of sensory and motor blockade was similar between the two groups.

Limitations of the study

This meta-analysis has limitations such as heterogeneity in research designs, discrepancies in dexmedetomidine and fentanyl doses, and variations in patient demographics. The included studies had inconsistent methodology, which could affect the credibility of the aggregated data.

CONCLUSION

The conclusions of this study have implications for policy, research, and practice. The comparable onset of sensory blockade between 0.5% levobupivacaine with fentanyl and dexmedetomidine and the superior prolongation of the sensory blockade and post-operative analgesia suggest that dexmedetomidine may be a better adjuvant in lower extremity surgery. This could impact physicians' decisions to use dexmedetomidine for patient

comfort and recovery. The results support the use of dexmedetomidine in anesthetic procedures, which could update recommendations for post-operative pain management. This study showed heterogeneity, so future research should investigate demographic characteristics, doses, and combinations to improve adjuvant selection and patient outcomes in different surgical settings.

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