RESEARCH

Intrathecal Dexmedetomidine-Fentanyl Combination versus Fentanyl Alone as Adjuvant to Bupivacaine in Spinal Anesthesia: A Comparative Study at Haji Adam Malik General Hospital

Firdaus Saputra[✉*], Tasrif Hamdi[**], Rr Sinta Irina[***]

[*]Faculty of Medicine, Universitas Sumatera Utara/Adam Malik General Hospital, Medan, Indonesia
[**]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[***]Study Program of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Sumatera Utara/Adam Malik General Hospital, Medan, Indonesia

[✉]Correspondence: firdaussaputra3248@gmail.com

ABSTRACT

Background: Spinal anesthesia is a regional analgesia that blocks nerve cells in the subarachnoid space by local anesthetic drugs. Bupivacaine is the most common agent, however, the duration of analgesia is often short. However, this advantage is hampered by the limited duration of spinal anesthesia and the uncomfortable postoperative period when the effect wears off. To prolong the duration of analgesia, various drugs such as opioids and α2 adrenergic agonists can be used as adjuvants for intrathecal local anesthetics to improve the quality of spinal anesthesia. One of the most widely used opioids is fentanyl, while the α2 adrenergic agonist is dexmedetomidine.

Objective: To analyze the difference in effectiveness of the combination of dexmedetomidine 5µg and fentanyl 25µg intrathecally with fentanyl 25µg as an adjuvant to bupivacaine in spinal anesthesia.

Method: This study is a double-blind randomized clinical trial to assess the comparison of the combination of dexmedetomidine 5µg and fentanyl 25µg intrathecally with fentanyl 25µg as an adjuvant to bupivacaine on the onset of block, duration of action, and side effects in surgery with spinal anesthesia.

Results: There were 32 samples with a distribution of 16 samples in each group. There was a significant difference in sensory and motor duration ($p<0.001$). The average sensory duration in the fentanyl group was 2 hours 45 minutes, and in dexmedetomidine + fentanyl, 4 hours 25 minutes. In comparison, the motor duration in the fentanyl group was 2 hours 30 minutes, and in the dexmedetomidine + fentanyl was 4 hours 2 minutes.

Conclusion: There is a comparison of the effectiveness of administering dexmedetomidine 5 mcg + fentanyl 25 mcg intrathecally and fentanyl 25 mcg intrathecally as an adjuvant to 0.5% bupivacaine in the spinal, where the dexmedetomidine group had a longer duration of anesthesia than the fentanyl group.

Keywords: dexmedetomidine; fentanyl; motor duration; sensory duration; spinal anesthesia

INTRODUCTION

With benefits including a quick onset of the working block, cost effectiveness, convenience of administration, a low incidence of side effects, and a shorter recovery period after anesthesia, spinal anesthesia is a safe and dependable anesthetic technique for both lower extremities and abdominal surgery. In contemporary surgical practice, spinal anesthesia is the favored option due to its numerous benefits over general anesthesia. Deep muscle relaxation, decreased intraoperative blood loss, improved safety for patients with respiratory conditions, reduced perioperative morbidity and mortality in high-risk patients, an earlier return of gastrointestinal function following surgery, suppression of the neuroendocrine response to surgery, superior analgesia compared to opioids in the postoperative period, and a decrease in the hypercoagulable state linked to surgery are some of the benefits.[1,2]

The short duration of spinal anesthetic and the unpleasant postoperative period when its effects wear off, however, negate this benefit. Higher doses of local anesthetic drugs can result in unfavorable hemodynamic abnormalities, such as bradycardia and hypotension, because of high concentrations, which are used to prolong the duration of analgesia. To enhance the quality of spinal anesthesia, a variety of medications, including opioids and α2 adrenergic agonists, can be administered as adjuvants for intrathecal local anesthetics. Fentanyl is one of the most widely utilized opioid classes, whereas dexmedetomidine is an α2 adrenergic agonist. Fentanyl is an opioid agonist that binds to the lipophilic μ receptor. Fentanyl reduces the release of substance P, a nociceptive transmitter, by binding to opioid receptors in the brain and spinal cord when administered intrathecally. The administration of intrathecal fentanyl has a faster onset of action with a shorter duration of action compared to morphine, making it widely used as a neuraxial opioid. Dexmedetomidine is a highly selective adrenergic receptor agonist for the α2 adrenergic receptor. Dexmedetomidine appears to exhibit better local anesthetic adjuvant properties for neuraxial blockade compared to clonidine.[1,2,3]

The sedative and analgesic effects of fentanyl and dexmedetomidine can intensify when they mix. Fentanyl and dexmedetomidine combined can have more potent analgesic and sedative effects. Without increasing the dosage of each medication, this combination is frequently used to improve the quality of sedation and lower the possibility of adverse effects. Dexmedetomidine can lessen the requirement for fentanyl, which lowers the possibility of opioid side effects such as constipation and respiratory depression.[4,5]

Because of its hemodynamic stabilizing properties, dexmedetomidine can lessen some of the hemodynamic alterations that fentanyl may cause. Despite not affecting breathing, dexmedetomidine and fentanyl together can raise the risk of respiratory depression, particularly in individuals with compromised lung function or at high dosages. Dhyva et al., discovered that in patients having cesarean sections, 25 μg of fentanyl extended the time that bupivacaine-induced sensory suppression lasted. Through distinct mechanisms, local anesthetics and opioids both have antinociceptive effects at the spinal cord. Fentanyl provides its effects through the opening of potassium ion channels and reducing calcium ion

influx, causing inhibition of transmitter release. Fentanyl also has a direct postsynaptic effect, causing hyperpolarization and a decrease in neuronal activity. Bupivacaine primarily works by inhibiting voltage-gated sodium channels on the axonal membrane, disrupting synaptic transmission by inhibiting presynaptic calcium ion channels, and affecting nerve conduction. The synergy between bupivacaine and fentanyl may be explained by this combination. When used as an adjuvant to bupivacaine, intrathecal fentanyl prolongs sensory blockade without extending motor blockade. The use of intrathecal fentanyl (0.2 μg/kg) was superior in prolonging postoperative pain relief with lower postoperative pain scores and fewer side effects, according to the study by Abdel Rady et al. When compared to midazolam, intrathecal fentanyl demonstrated superior outcomes in terms of delayed block onset, longer duration of sensory and motor block, and longer duration of full and efficient analgesia.[6,7]

METHOD

This study is a clinical trial with a double-blind randomized method, aimed at assessing the comparison of administering a combination of dexmedetomidine 5μg and fentanyl 25μg intrathecally with fentanyl 25μg as an adjuvant to bupivacaine in terms of block onset, duration of action, and side effects in surgery with spinal anesthesia. This research was conducted at the Central Surgical Installation and Emergency Surgical Room of Haji Adam Malik General Hospital Medan. The research began after the researcher obtained ethical approval from the Research Ethics Committee of the Universitas Sumatera Utara. Sample selection and data collection were carried out until the minimum sample size was met. The subjects of this study are all patients undergoing lower abdomen / lower extremity surgery with spinal anesthesia at the Central Surgical Installation and Emergency Operating Room of Haji Adam Malik General Hospital Medan. The subjects in this study are a portion of the population that meets the inclusion and exclusion criteria. The research subjects will be randomly divided into two groups, namely the group receiving dexmedetomidine 5 mcg + fentanyl 25 mcg intrathecally and the group receiving fentanyl 25 mcg intrathecally as an adjuvant to bupivacaine in spinal anesthesia. A total of 32 subjects met the inclusion and exclusion criteria, with no subjects lost to follow-up. The patients underwent surgery and were followed up one day after the operation. The patient's outcomes from medications were assessed by evaluating onset, duration, and haemodynamics. Randomization was conducted by the researcher using a computerized randomization method with www.randomizer.org.

RESULTS

This study obtained a sample of 16 samples per group, with a total sample of 32 samples. In this study, the basic characteristics reported include age, gender, and PS-ASA. In Table 1, it is noted that the age of the fentanyl group has a mean value of approximately 44.37 ± 13.99 years, while the dexmedetomidine and fentanyl group has a mean value of approximately 44.81 ± 10.98 years. The distribution of gender in the fentanyl group was 9 males (56.3%) and 7 females (43.8%), while in the dexmedetomidine and fentanyl group, there were 10 females (62.5%) and 6 males (37.5%). The PS-ASA distribution in the fentanyl group showed ASA 1 in 10 people (62.5%) and ASA 2

in 6 people (37.5%), while in the dexmedetomidine and fentanyl group, ASA 1 was found in 7 people (46.7%) and ASA 2 in 9 people (56.3%).

An analysis of the onset difference between the fentanyl group and the dexmedetomidine and fentanyl group was conducted. The difference analysis used a T-test because it was known that all onset data were normally distributed.

Both sensory onset and motor onset show significant differences (p 0.05<0.001) between the fentanyl group and the dexmedetomidine and fentanyl group. An analysis of the duration difference between the fentanyl group and the dexmedetomidine and fentanyl group was conducted. The difference analysis used the T-test because it is known that all duration data are normally distributed. (Table 2)

All duration data show a significant difference (p 0.05<0.001) between the fentanyl group and the dexmedetomidine and fentanyl group. A hemodynamic difference analysis was conducted between the combination group and the bupivacaine group. The difference analysis used a T-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. (Table 3)

The hemodynamic characteristics of dexmedetomidine + fentanyl and the hemodynamic characteristics of fentanyl obtained a p-value > 0.05, indicating no significant difference between the two groups. (Table 4)

The characteristics of heart rate in fentanyl and the characteristics of HR in dexmedetomidine and fentanyl obtained a p-value > 0.05, indicating no significant difference between the two groups. (Table 5)

The characteristics of respiratory rate and SpO2 in fentanyl and dexmedetomidine and fentanyl showed a p-value > 0.05, indicating no significant difference between the two groups. A descriptive analysis of the incidence of side effects between the combination group and the bupivacaine group was conducted using the Crosstab test, followed by the presentation of data in table form. (Table 6)

Side effects were found in the fentanyl group, with nausea and vomiting in 4 people (25%), hypotension in 5 people (31.3%), and shivering in 4 people (25%), whereas in the dexmedetomidine group, nausea and vomiting were found in 7 people (43.8%), hypotension in 8 people (50%), shivering in 6 people (37.5%), and injection site pain in 4 people (25%). Based on the p-value, there was no significant difference between the groups. (Table 7)

Table 1. Characteristics of the research sample

Characteristic	Fentanyl group (n=16)	Dexmedetomidine and fentanyl group (n=16)	p- Value
Age (Year)			
Mean±SD	44.37 ± 13.99	44.81 ± 10.98	0.105
Gender			
Male	9 (56.3%)	6 (37.5%)	0.251
Female	7 (43.8%)	10 (62.5%)	
PS-ASA			
1	10 (62.5 %)	7 (46.7 %)	0.211
2	6 (37.5 %)	9 (56.3 %)	

Table 2. Results of the onset difference test between groups

Characteristic	Fentanyl (n=16)	Group	Dexmedetomidine and fentanyl group (n=16)	p-value
Onset sensoric (minute)				
Mean±SD	3.41 ± 0.16		3.28 ± 0.23	<0.001[a]
Onset motoric (minute)				
Mean±SD	3.32 ± 0.23		3.40 ± 0.23	<0.001[a]

[a] T-test

Table 3. Results of the test for duration differences between groups

Characteristics	Fentanyl group (n=16)	Dexmedetomidine and fentanyl group (n=16)	p-value
Sensoric duration (minutes) Mean±SD	165.56 ± 6.71	265.81 ± 24.36	<0.001[a]
Motoric duration (minutes) Mean±SD	150.93 ± 9.71	241.75 ± 9.71	<0.001[a]

[a]Uji T-test

Table 4. Demographic hemodynamic data between groups

Characteristics	Fentanyl group (n=16)	Dexmedetomidine and fentanyl group (n=16)	p–value
SBP T0	128.50 ±11.10	126.75 ± 9.34	0.852
SBP T0	69.87 ± 8.20	79.56 ± 9.28	0.215
SBP T1	107.18 ± 12.42	100.12 ± 13.01	0.619
SBP T1	68.81 ± 8.15	78 ± 8.09	0.064
SBP T2	116.62 ± 10.21	118.18 ± 6.06	0.191
SBP T2	69.87 ± 7.42	76.93 ± 8.27	0.062
SBP T3	123.12 ± 3.64	118.43 ± 8.50	0.064
SBP T3	71.87 ± 6.80	76.50 ± 8.78	0.074
SBP T4	118.06 ± 8.51	123 ± 9.08	0.071
SBP T4	74.62 ± 6.83	77.75 ± 8.20	0.194

Uji T-test

Table 5. Demographic data comparison of heart rate between groups

Characteristics	Fentanyl group (n=16)	Dexmedetomidine and fentanyl group (n=16)	p – value
HR T0	80.50 ± 8.04	79.50 ± 9.33	0.489
HR T1	79.43 ± 8.56	76.43 ± 8.56	0.056
HR T2	75.62 ± 8.29	75.37 ± 9.56	0.838
HR T3	80.06 ± 4.26	79.62 ± 4.97	0.430
HR T4	80.43 ± 6.05	80.62 ± 5.13	0.87

Uji T-test

Table 6. Demographic data comparison of respiratory rate and SpO2 between groups

Characteristics	Fentanyl group (n=16)	Dexmedetomidine and fentanyl group (n=16)	p – value
RR T0	18.06 ± 0.92	18.37 ± 0.95	0.333
RR T1	18.18 ± 1.81	18 ± 1.03	0.083
RR T2	18.53 ± 0.61	18.72 ± 0.96	0.333
RR T3	18.12 ± 0.80	18.06 ± 0.85	0.270
RR T4	18.18 ± 1.22	18 ± 1.22	0.383
SpO2 T0	98.27 ± 1.68	97 ± 1.30	0.485
SpO2 T1	98.25 ± 0.93	98.37 ± 1.02	0.718
SpO2 T2	97.60 ± 1.68	98.13 ± 1.68	0.580
SpO2 T3	98.37 ± 1.02	98.25 ± 0.93	0.333
SpO2 T4	98.31 ± 1.01	98.37 ± 1.02	0.432

T-test

Table 7. Results of the adverse effect analysis between groups

Characteristics	Fentanyl group (n=16)	Dexmedetomidine and fentanyl group (n=16)	p - value
Sedation RSS Score 4	0	0	
Bradycardia	0	0	
Nausea and vomiting	4 (25%)	7 (43.8%)	<0.005
Hypotension	5 (31.3%)	8 (50%)	<0.005
Shivering	4 (25%)	6 (37.5%)	<0.005
Hypoventilation	0	0	
Desaturation	0	0	
Paralysis	0	0	
Paresthesia	0	0	
Diplopia	0	0	
Nystagmus	0	0	
Headache	0	0	
Pain in the injection site	5 (25%)	4 (25%)	<0.005

DISCUSSION

By using a local anesthetic to inhibit nerve cells in the subarachnoid area, spinal anesthesia provides regional analgesia. With a strong level of analgesia, the patient remains conscious, adequate muscle relaxation, less bleeding from surgical wounds, a lower risk of aspiration in patients with a full stomach, and a quicker recovery of gastrointestinal function, this anesthesia technique has gained popularity due to its simplicity, effectiveness, safety for the nervous system, and non-harmful drug concentration in the plasma. The ideal type of local anesthetic is a drug with a rapid onset, long duration, and a high blockade that can be predicted to match the estimated duration of the surgery to be performed. Various efforts have been made to increase the onset speed and prolong the duration of spinal anesthesia. Among them, by adding other anesthetic drugs such as ketamine, midazolam, dexmedetomidine, and neostigmine to local anesthesia.[8,9,10]

In this study, it was found that the basic characteristics reported in this study consisted of age, gender, and PS-ASA. In Table 1, it was found that the age of the fentanyl group had a mean value of approximately 44.37 ± 13.99 years, and the dexmedetomidine and fentanyl group had a mean value of approximately 44.81 ± 10.98 years. The distribution of gender in the fentanyl group was 9 males (56.3%) and 7 females (43.8%), while in the dexmedetomidine and fentanyl group, there were 10 females (62.5%) and 6 males (37.5%). The PS-ASA distribution in the fentanyl group showed ASA 1 in 10 people (62.5%) and ASA 2 in 6 people (37.5%), while in the dexmedetomidine and fentanyl group, ASA 1 was found in 7 people (46.7%) and ASA 2 in 9 people (56.3%).[9,10]

A significant difference between the groups was shown by a p-value of less than 0.001 in the examination of the sensory and motor onset differences between the fentanyl group and the dexmedetomidine and fentanyl group. This is in line with Yudi Wijaya's study, in which she evaluated the effects of fentanyl 25 mcg and dexmedetomidine 5 mcg as adjuvants in spinal anesthesia with levobupivacaine 10 mg. She discovered that the onset of anesthesia with dexmedetomidine was quicker than with fentanyl. A similar finding was also obtained in a study conducted by Safari et al., where the researchers compared fentanyl 25 mcg + bupivacaine 12.5 mg with dexmedetomidine 5 mcg + bupivacaine 12.5 mg. In that study, it was found that the dexmedetomidine group had a faster onset compared to fentanyl as an adjuvant in spinal anesthesia using bupivacaine.[11]

A significant difference was shown by a p-value of less than 0.001 in the examination of the sensory and motor duration differences between the ketamine and dexmedetomidine groups. This is comparable to Yudi Wijaya's work, in which the researcher evaluated the adjuvants fentanyl 25 mcg and dexmedetomidine 5 mcg in spinal anesthesia with levobupivacaine 10 mg. With an average duration of 303 minutes for dexmedetomidine and 202 minutes for fentanyl, it was discovered that the duration of anesthesia with dexmedetomidine was longer than that with fentanyl. This is similar to the research conducted by Syed et al., where the researchers compared three adjuvants: the first group received bupivacaine 10 mg + fentanyl 25 mcg, the second group received bupivacaine 10 mg + dexmedetomidine 5 mcg + 0.5 ml normal saline, and the third group received 2 ml 10 mg + 5 mcg

dexmedetomidine + fentanyl 25 mcg. It was found that the duration of anesthesia in the third group was longer compared to the other two groups.[12,13]

In the study by Khosravi et al., the researchers compared fentanyl 24 mcg + bupivacaine 10 mg with dexmedetomidine 5 mcg + bupivacaine 10 mg. It was found that the duration of analgesia with dexmedetomidine was 428 minutes, while fentanyl lasted for 273 minutes. A similar finding was obtained in the study conducted by Safari et al., where the researchers compared fentanyl 25 mcg + bupivacaine 12.5 mg with dexmedetomidine 5 mcg + bupivacaine 12.5 mg. In that study, it was found that the dexmedetomidine group had a longer duration of action compared to fentanyl as an adjuvant in spinal anesthesia using bupivacaine.[13]

The analgesic mechanism of dexmedetomidine in neuraxial anesthesia is responsible for the extended duration of analgesia in spinal anesthesia. Through the release of C-fiber neurotransmitters and the hyperpolarization of postsynaptic neurons in the spinal cord's dorsal horn, dexmedetomidine causes analgesic effects via the spinal cord's α2 receptor. Dexmedetomidine, as an α2 receptor agonist, has various effects as an adjuvant in neuraxial anesthesia, including: (1) reduced onset time of sensory and motor blockade; (2) increased sensory blockade; (3) prolongation of postoperative analgesia duration and reduction of total analgesia dosage; (4) decrease in the need for rescue analgesia. The mechanism of action of dexmedetomidine depends on the dose used.[10,12]

By binding to mu receptors in the spinal cord's gelatinous substance, opioids given intrathecally provide analgesic effects. G-protein-coupled receptors are where fentanyl will attach itself. The competitive binding of opioids to particular pain-inducing receptors causes afferent sensory neurons to become hyperpolarized. The capacity to activate the pain management system from the midbrain to the spinal cord's dorsal horn via the ventromedial rostral medulla and directly prevent the passage of nociceptive signals from the dorsal horn. Because fentanyl effectively modifies pain perception and suppresses the pain pathway, this mechanism produces an analgesic effect. The effects generated are significantly influenced by variables like dosage, lipophilicity, injection site, and the surrounding environment.[14,15]

Side effects were found in the fentanyl group, including nausea and vomiting in 4 people (25%), hypotension in 5 people (31.3%), and shivering in 4 people (25%), while in the dexmedetomidine group, nausea and vomiting were found in 7 people (43.8%), hypotension in 8 people (50%), shivering in 6 people (37.5%), and injection site pain in 4 people (25%). Some studies said that the side effects of fentanyl like respiratory depression. Fentanyl can slow down or stop breathing, which is the most dangerous side effect, especially if the dose is too high. Nausea and vomiting: these are common side effects, especially at the initial dose or after long-term use, sedation or drowsiness: users may feel very drowsy or weak after receiving intrathecal fentanyl. Dizziness or loss of balance: this side effect can occur due to a drop in blood pressure or direct impact on the central nervous system. Hypotension (low blood pressure): Fentanyl can cause significant drops in blood pressure,

especially in patients who already have heart problems. Headache: Some patients reported experiencing headaches after the administration of intrathecal fentanyl. Pruritus (itching): itching or skin rashes can occur in some people. Bowel obstruction: fentanyl can slow down bowel function, causing constipation or even bowel obstruction. Seizures: at high doses or improper use, fentanyl can cause seizures.

Dexmedetomidine is a strong α2-adrenergic agonist that works in part by increasing parasympathetic flow and decreasing sympathetic flow from the brainstem's locus coeruleus. The medullary vasomotor center's negative feedback receptors are activated, which reduces catecholamine output and mediates its sympatholytic effects. Bradycardia and hypotension may be seen when using dexmedetomidine because of the decrease in norepinephrine release and possible baroreflex activation. According to reports, these adverse effects are brought on by high doses or a brief loading time and are directly tied to the dosage and/or the method of giving the substance.[14,15]

Although the exact mechanism of action is yet unknown, opioids can directly stimulate the vestibular apparatus. By stimulating mu-opioid and delta-opioid receptors in the central chemoreceptor trigger zone, endogenous opioids seem to play a role in the process of opioid-induced vomiting. The medullary chemoreceptor trigger zone appears to be the starting point for opioid-induced vomiting, and tolerance at the level of central opioid receptors may be different from tolerance at receptors outside the central nervous system. Tolerance to the emetic activity of opioids may develop sooner or be more severe if the interaction between opioid agonists and opioid receptors in the chemoreceptor trigger zone for a particular opioid is comparatively protracted compared to its peripheral actions.[10,12]

CONCLUSION

There is a difference in the effectiveness of administering dexmedetomidine 5 mcg + fentanyl 25 mcg intrathecally and fentanyl 25 mcg intrathecally as an adjuvant to 0.5% Fentanyl has non-specific receptors in the body, causing many side effects. Bupivacaine in spinal anesthesia, where the dexmedetomidine group had a longer duration of anesthesia compared to the fentanyl group.

REFERENCES

1. Sun, S., Wang, J., Bao, N., Chen, Y., Wang, J. Comparison of Dexmedetomidine and Fentanyl as local anesthetic adjuvants in spinal anesthesia: a systematic review and meta-analysis of randomized controlled trials. Drug Design Development and Therapy;2017;11:3413-3424
2. Gupta, R., Verma, R., Bogra, J., Kohli, M., Raman, R., Kushwaha, JK. A comparative study of intrathecal Dexmedetomidine and Fentanyl as adjuvants to bupivacaine. Journal of Anaesthesiology Clinical Pharmacology;2011;27(3)
3. Safari, F., Aminnejad, R., Mohajerani, S.A., Farivar, F., Mottaghi, K., Safdari, H. Intrathecal Dexmedetomidine and Fentanyl as adjuvant to bupivacaine in duration of spinal block in addicted patients. Anesth Pain Med;2016;6(1):e26714

4. Divya, V.S., Raghu, R., Indira, P., Roy, S. Comparison of Dexmedetomidine and Fentanyl as adjuvants to 0,5% hyperbaric bupivacaine in spinal anesthesia in elective lower abdominal surgeries. Indian Journal of Clinical Anaesthesia;2021;8(2):257-264
5. Weerink, M.A., Struys, MM., Hannivoort, LN., Barends, CR., Absalom, AR., Colin, P. Clinical pharmacokinetics and pharmacodynamics of Dexmedetomidine. Clin Pharmacokinet;2017;56:893-913
6. Nayagam HÁ, Singh NR, Singh HS. A prospective randomised double blind study of intrathecal Fentanyl and Dexmedetomidine added to low-dose bupivacaine for spinal anesthesia for lower abdominal surgeries. Indian J Anaesth. 2014;58:430---5. 16.
7. Setiawan D, Perbandingan Mula Kerja dan Lama Kerja Blokade Antara Penambahan Ketamin dengan Fentanyl pada Bupivakain Sebagai Anestesi Spinal. Tesis. Universitas Negeri Sebelas Maret. Surakarta. 2012
8. Safari, F., Aminnejad, R., Mohajerani, S.A., Farivar, F., Mottaghi, K., Safdari, H. Intrathecal Dexmedetomidine and Fentanyl as adjuvant to bupivacaine in duration of spinal block in addicted patients. Anesth Pain Med;2016;6(1):e26714
9. Bgrami, Syed A. H.; Kumar, Manoj; Singh, Dipali[1]; Priye, Shio[2]. A comparison of Fentanyl, Dexmedetomidine, and a combination of Fentanyl with Dexmedetomidine on the quality of subarachnoid block and postoperative analgesia: A double-blind controlled study. Indian Journal of Anaesthesia 66(Suppl 4):p S220-S224, | DOI: 10.4103/ija.ija_701_21
10. Khosravi F, Sharifi M, Jarineshin H. Comparative study of Fentanyl vs Dexmedetomidine as adjuvants to intrathecal bupivacaine in cesarean section: a randomized, double-blind clinical trial. Journal of Pain Research. 2020 Oct 7:2475-82.
11. Solanki SL, Goyal VK. Neuraxial Dexmedetomidine: wonder drug or simply harmful? Anesthesiology and pain medicine. 2015 Apr 1;5(2).
12. Nayak A, Ninave S, Tayade S, Tayade H. Intrathecal Adjuvant Midazolam Versus Fentanyl With Hyperbaric Bupivacaine for Post-operative Analgesia in Women Undergoing Total Abdominal Hysterectomy. Cureus. 2023 Jun 17;15(6):e40565. doi: 10.7759/cureus.40565. PMID: 37465806; PMCID: PMC10351601.
13. Li Z, Tian M, Zhang CY, et al. A randomised controlled trial to evaluate the effectiveness of intrathecal bupivacaine combined with different adjuvants (Fentanyl, clonidine and Dexmedetomidine) in caesarean section. Drug Res (Stuttg). 2015;65:5816.
14. D. S. Carollo, B. D. Nossaman, and U. Ramadhyani, “Dexmedetomidine: a review of clinical applications,” *Current Opinion in Anaesthesiology*, vol. 21, no. 4, pp. 457–461, 2008.
15. W. M. Abdelmageed, R. Shabana, A. Nassar, K. Elquesny, and H. Abushama, “Analgesic properties of a Dexmedetomidine infusion after uvulopalatopharyngoplasty in patients with obstructive sleep apnea,” *Saudi Journal of Anaesthesia*, vol. 5, no. 2, p. 150, 2011.