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Article

Comparison of "Bupivacaine, Bupivacaine + Dexmedetomidine and Bupivacaine + Dexamethasone" Applications as Ultrasound-Guided Transversus Abdominis Plain Block Approach in Relieving Pain after Cesarean Section: Is Body Mass Index Effective Factor?

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Abstract: Background: The transversus abdominis plane (TAP) block has gained increasing importance as a very effective pain relief in for caesarean section. This study aimed to compare bupivacaine (Group B), bupivacaine with dexmedetomidine (Group BD) and bupivacaine with dexamethasone (Group BDx) applied in ultrasound-guided TAP block in the treatment of CS postoperative pain. **Material and Method:** American Society of Anesthesiologists I and II pregnant women who underwent cesarean section were included in the study. Forty patients were admitted in each group. All patients were applied TAP block with ultrasound guidance by administering the medications of the group in which they were included. **Results:** Body mass index (BMI) and operation duration were higher in Group B ($p=0.01$ and 0.004 , respectively). Instant tramadol requirement and amount were higher in Group B at some of follow up times. Patient satisfaction scale were better in Group BD and Group BDx. **Conclusion:** TAP block significantly reduces pain after cesarean section, prolongs the time to first analgesic request, and reduces the need for additional opioid analgesics. The addition of adjuvant to the TAP block usually improves the postoperative clinical condition. However, some special conditions such as body mass index (BMI) may negatively affect the clinical situation. Comprehensive, standardized, randomized controlled studies are needed to compare results under different conditions.

Keywords: bupivacaine; dexmedetomidine; dexamethasone; post-operative analgesia; caesarean section

1. Introduction

Caesarean section (CS) is one of the most common surgeries and usually causes moderate to severe pain for up to 48 hours [1]. The rate of CS, which is a life-saving surgical procedure when certain complications occur during pregnancy and birth, has exceeded 20% worldwide [2,3]. More than 100% of all births occur via CS. However, this is a major surgery and is associated with immediate maternal and perinatal risks [2]. Pain control after CS has crucial importance, especially in the first 24 hours, to facilitate early ambulation and the establishment of breastfeeding [4]. In this context, many studies are being conducted to increase the TAP blockage duration. Although commonly used nonsteroidal anti-inflammatory drugs and paracetamol can only supplement other modes of analgesia, they are not sufficient on their own population [5].

The transversus abdominis plane (TAP) block has gained increasing importance as a very effective pain relief in abdominal surgery since Rafi's application in 2001 [6]. In the TAP block, local anesthetic solution is applied between the transverse and internal oblique muscles of the abdominal wall at the T7-L1 level (Figure 1). The solution anesthetizes the nerves operating in this plane [7]. This reduces post-operative pain from lower abdominal surgeries, including cesarean sections [8]. TAP

block is usually applied with the help of ultrasonography in order to apply it to the most appropriate anatomical area and ultimately ensure the highest level of effectiveness [4].

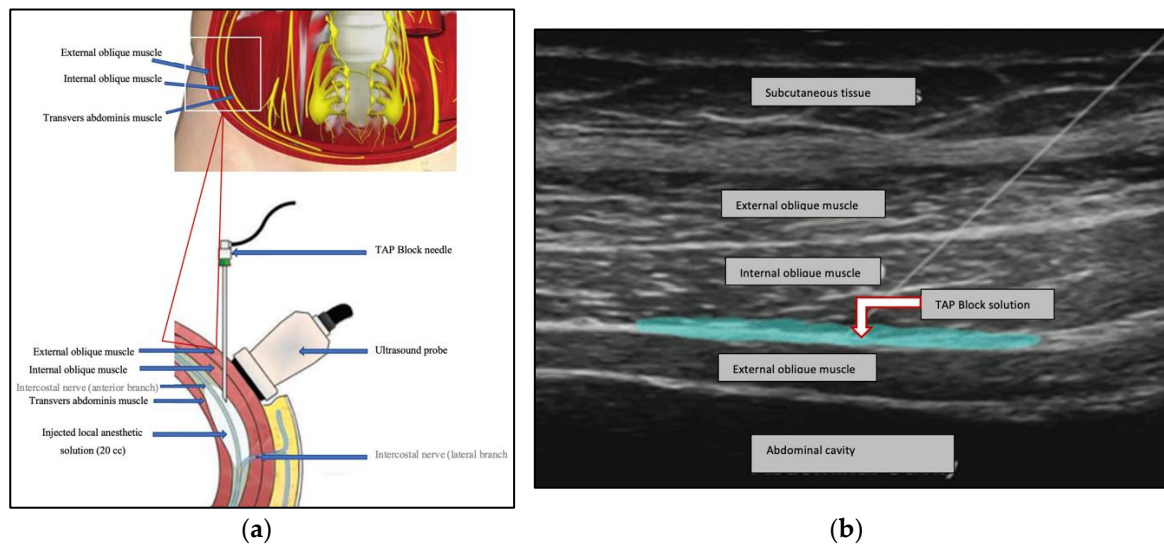


Figure 1. Transversus abdominis plane block application: a. Schematic demonstration, b. Ultrasound image. Modified from ref. 7.

A variety of anesthetic agents such as bupivacaine, levobupivacaine and ropivacaine is used for TAP block [8]. As important disadvantages, the drug solution may be absorbed systemically and may cause adverse effects such as cardiotoxicity and neurotoxicity [2]. Secretion into breast milk is an additional concern in this population [9]. The drugs used in TAP block have also a short-term analgesic effect and only relieve somatic pain [9,10].

Various adjuvants such as opioids, ketamine, clonidine, and alpha-2 agonists (i.e. dexmedetomidine) have been used to increase the duration of the analgesic effect of the TAP block⁸. Furthermore, various studies have shown that adequate analgesic use reduces opioid consumption and alleviates nausea and sedation in the postoperative period [1].

Postoperative CS pain arises mainly from somatic and visceral components. Surgical incision of the tissue leads to somatic pain, while the visceral pain is mainly associated with inflammation¹¹. TAP block alleviates somatic pain by inhibiting neural afferents from T7-L1 [4]. Dexmedetomidine is a highly selective central alpha-2 adrenergic agonist. It strengthens local anesthetic effects and prolongs analgesic duration by blocking the transmission of nerve signals through C and A delta fibers [4,12]. Dexamethasone produces analgesia thanks to its anti-inflammatory properties. It also potentiates the effect of local anesthetics [13].

Bupivacaine is one of the widely used local analgesics [14]. Dexmedetomidine is commonly used as an adjuvant to local anesthetics in many studies [4,15,16].

There have been efforts to increase the duration of TAP block, multiple additives have been added to local anesthetic solutions used for this block. Opioids, ketamine, clonidine and dexmedetomidine are the various additives that have been used to see if they increase the duration of analgesic effect of TAP block [8].

This study aimed to compare the effectiveness of dexamethasone and dexmedetomidine used as adjuvants to bupivacaine in ultrasound-guided TAP block in the treatment of CS postoperative pain. According to our current knowledge, there is no study comparing these two factors as an adjuvant to bupivacaine.

2. Materials and Methods

Study Design

The study was carried out between September 2019 and February 2020 at Hatay Mustafa Kemal University after obtaining ethical approval from Clinical Research Ethics Committee (meeting date: 20.02.2020, decision no: 05). Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki [17]. A total of 120 pregnant female, aged between 18 and 42 (mean 30.1 ± 5.6), patients who were planned to undergo CS under spinal anesthesia were included in the study.

Pregnant women with American Society of Anesthesiologists (ASA) I or II score who underwent CS surgery by applying spinal anesthesia with 2-2.2 ml of 0.5% heavy bupivacaine from the L3-5 interval through a Pfannenstiel incision were included in the study. Exclusion criteria were applied in case of any of the following situations: Refusal to participate in the study, known allergy to local anesthetics/opioids/nonsteroidal anti-inflammatory drugs, infection at the needle entry site for the block, recent glucocorticoid use, diabetes, pregnancy-induced hypertension, chronic pain medication use and body mass index (BMI) >35 . Subjects included in the study were randomly assigned to three groups using a computer-generated sequence of random numbers, regardless of their demographic characteristics.

Patients were equally (40 per group) allocated to three TAP block groups as follows:

1. Group-B: Bupivacaine 0.5% 10ml + physiological saline 10ml,
2. Group-BD: Bupivacaine 0.5% 10ml + physiological saline 9ml + dexmedetomidine 1ml ($1 \mu\text{g/kg}$),
3. Group-BDx: Bupivacaine 0.5% 10ml + physiological saline 9ml + dexamethasone 1ml (4 mg).

Anesthesia Technique

Patients included in the study were informed about the procedures. In the operating room, electrocardiography, pulse oximetry and noninvasive blood pressure monitoring were performed on all patients from the beginning of the procedure until they left the operating room.

At the end of the CS surgery TAP block application was performed bilaterally, with 20 ml of medication administered to each side, under ultrasonography (SonoSite M-Turbo) guidance following using according to the group assignment. For scanning, a linear multi-frequency (12 MHz) converter was used.

TAP block application was performed as previously described [1]. Briefly: The procedure was performed with the patient in the supine position and with a single injection. TAP block solution was injected into the plane between the internal oblique and transversus abdominis muscles in the lateral abdominal wall region between the lower costal margin and the iliac crest. Then the same process was performed on the other side. After these procedures, the patients were transferred to the post-anesthesia care unit (Figure 1).

Monitoring of Patients

Patients transferred to the post-anesthesia care unit were routinely given paracetamol (1 mg) intravenously for 24 hours, every 6 hours. Visual Analogue Score (VAS) scores were evaluated at 0, 1, 4, 8, 16 and 24 hours. VAS scores were evaluated in both sitting and supine positions, and the average value of these two was used to determine analgesic requirement. Those with a VAS score ≥ 4 were given 0.5 mg/kg tramadol intravenously.

Instant and total analgesic consumption as well as complications were monitored through intermittent recordings during the first 24 hours of the postoperative period. The time from the completion of local anesthetic administration to the first analgesic request was defined as the analgesia duration.

Time to first request for analgesic was expressed as the primary outcome of the study. The secondary outcomes were total postoperative analgesic consumption, postoperative nausea and vomiting, and patient satisfaction. Patient satisfaction was evaluated regarding pain relief after 24 hours. It was evaluated whether there was nausea and vomiting during the follow-up period. At the end of 24 hours, the block area was examined for signs of any infection, hematoma, or other side effects such as hypotension, bradycardia, tinnitus, dry mouth.

Statistical Analysis

For patients undergoing cesarean section, a Randomized Controlled Treatment research design was applied in which the primary outcome variable VAS scale value would be compared according to Bupivacaine, Bupivacaine + Dexmedetomidine and Bupivacaine + Dexamethasone treatment protocols (group details are given above). The number of patients between the three groups was determined according to the VAS scale mean difference value with an effect size of 0.2 Cohen's d, which is considered to be the minimum clinically significant one, and with a maximum power of 5% and a minimum power of 80% of type I error.

Statistical analysis of the data was performed using IBM SPSS Version 21 and MedCalc statistical package program. Due to the suitability of the Central Limit Theorem, parametric tests were used for continuous measurements without normality testing [18]. However, since VAS and Satisfaction Scores were ordinal variables, non-parametric testing was used. When making statistical analysis of continuous data on scales, mean ± standard deviation, median and 25%-75% values are used. Frequency and percentage values were used to describe categorical variables.

One Way ANOVA test and Kruskal Wallis H statistics were used to compare continuous measurement averages in three groups. If a difference was detected, pairwise comparisons were evaluated with Tukey statistics as a Post Hoc test. Chi-Square test was used to evaluate the relationship between categorical variables. If a relationship was detected, z test statistics were used to evaluate the difference in pairwise ratio.

For statistical significance, p<0.05 was accepted.

3. Results

The ages of the pregnant women were between 18 and 42 years (mean 30.1±5.6, median 30). While the ASA score was 1 in 48.3%, it was 2 in 51.7%. There was no statistically significant difference between the three groups in terms of mean of age and ASA score. The mean value of body mass index (BMI) and operation duration of all groups were 28.68±2.83 (median 28.65) and 70.6±15.5 minutes (median 70 minutes), respectively. Both were statistically significant between groups (p*=0.01 and 0.004, respectively). Block duration was also statistically significant between groups (p*=0.001) (Table 1).

Table 1. Socio-demographic characteristics and operation, and block times of the groups (n=120).

	Bupivacaine (n=40)	Bupivacaine +Dexmedetomidin (n=40)	Bupivacaine +Dexametazon (n=40)	p value*	p value** 1 vs 2, 1 vs 3, 2 vs 3
	Mean±SD	Mean±SD	Mean±SD		
Age	30.1±5.4	31.5±5.9	28.9±5.2	0.23	-
BMI	29.41±2.89	29.03±2.98	27.62±2.34	0.01	0.82, 0.01, 0.06
ASA score	n (%)	n (%)	n (%)		
I	19(47.5)	18(45)	21(52.5)	0.85	-
II	21(52.5)	22(55)	19(17.5)		
Operation duration	77.1±17.7	68±11.6	66.8±14.8	0.004	0.02, 0.007, 0.93
Block duration	10.9±2.4	9.1±1.5	9.2±2.4	0.001	0.001, 0.002, 0.91

* One-Way ANOVA test | Chi-square test, ** Post Hoc test-Tukey; p<0.05 is significant. BMI: body mass index above, ASA: American Society of Anesthesiologists, SD: Standard deviation.

While the 0th hour instant analgesic tramadol requirement was 12.5% in the BDx group, it was not required in the B and BD groups. This difference between the groups was significant ($p^*=0.005<0.05$; $p^{**}=0.02, 0.02<0.05$). While this difference was significant at the 1st and 8th hours, there was no significant difference at the 4th, 16th and 24th hours.

The total tramadol requirement was significant at the 0th, 1st and 4th hours, whereas there was no significant difference at the 8th, 16th and 24th hours.

While there was a significance at hour 0 in terms of both nausea and vomiting ($p^*=0.003<0.05$; $p^{**}=0.006, 0.03<0.05$) and the presence of other complications ($p^*=0.009<0.05$; $p^{**}=0.01, 0.04<0.05$), there was no significant relationship for both parameters at other follow-up hours. No significance was found in terms of total tramadol and total antiemetic requirements and nausea and vomiting (Table 2).

Table 2. Assessment of clinical relationship between treatment groups (n=120).

	Bupivacaine (n=40)	Bupivacaine +Dexmedetomidin (n=40)	Bupivacaine +Dexametazon (n=40)		
Hour	n(%)	n(%)	n(%)	p value*	p value** 1 vs 2, 1 vs 3, 2 vs 3
Instant analgesic tramadol requirement					
0	0(0)	0(0)	5(12.5)	0.005	- 0.02 0.02
1	2(5)	1(2.5)	10(25)	0.002	0.56 0.01 0.003
4	9(22.5)	9(22.5)	12(30)	0.67	-
8	18(45)	7(17.5)	16(40)	0.02	0.008 0.65 0.03
16	12(30)	13(32.5)	10(25)	0.75	-
24	1(2.5)	6(15)	2(5)	0.08	-
Total analgesic tramadol requirement					
0	0(0)	0(0)	5(12.5)	0.005	- 0.02 0.02
1	2(5)	1(2.5)	14(35)	0.001	0.56 0.001 0.001
4	11(27.5)	9(22.5)	20(50)	0.02	0.61 0.04 0.01
8	20(50)	16(40)	24(60)	0.2	-
16	21(52.5)	21(52.5)	27(67.5)	0.29	-
24	19(47.5)	23(57.5)	27(67.5)	0.20	-
Nausea and/or vomiting					
0	0(0)	1(2.5)	7(17.5)	0.003	0.31 0.006 0.03
1	5(12.5)	5(12.5)	9(22.5)	0.37	-
4	6(15)	9(22.5)	10(25)	0.52	-
8	8(20)	12(30)	10(25)	0.59	-
16	7(17.5)	12(30)	11(27.5)	0.39	-
24	7(17.5)	13(32.5)	11(27.5)	0.3	-
Complication					
0	0(0)	1(2.5)	6(15)	0.009	0.31 0.01 0.04
1	5(12.5)	3(7.5)	3(7.5)	0.67	-
4	2(5)	4(10)	1(2.5)	0.35	-
8	3(7.5)	3(7.5)	1(2.5)	0.55	-
16	0(0)	0(0)	1(2.5)	0.36	-
24	0(0)	1(2.5)	0(0)	0.377	-
Total analgesic tramadol requirement	21(52.5)	23(57.5)	27(67.5)	0.38	-
Total antiemetic requirement	10(25)	12(30)	13(32.5)	0.75	-
Nausea and/or vomiting	10(25)	12(30)	12(30)	0.85	-

* Chi-square test, ** z test; $p<0.05$ is significant.

Headache, hypotension, bradycardia, arrhythmia, tinnitus and numbness around the mouth were not observed in all three treatment groups.

While there was a significance at hour 0 in terms of instant analgesic tramadol usage amount ($p^*=0.04<0.05$), there was no significant relationship at other follow-up hours.

While there was a significance at hour 4 and 8 in terms of total analgesic tramadol usage amount ($p^*=0.003<0.05$ and $p^*=0.04<0.05$, respectively), there was no significant relationship at other follow-up hours.

For each treatment groups, 1st, 4th, 8th, 16th. and 24th hour the mean values of the instant antiemetic (mg) usage were same (10 ± 0) (Table 3).

Table 3. Evaluation of instantaneous analgesic and antiemetic use amounts between treatment groups (n=120).

	Bupivacaine (n=40)	Bupivacaine +Dexmedetomidin (n=40)	Bupivacaine +Dexametazon (n=40)		
Hour	Mean±SD	Mean±SD	Mean±SD	p value*	p value** 1 vs 2, 1 vs 3, 2 vs 3
Instant analgesic tramadol amount (mg)					
0	45±0	40±-	37.2±3.67	0.04	- 0.04 -
1	38.61±3.33	38.06±3.14	35.83±3.68	0.16	-
4	39.56±3.62	39.36±5.37	36.37±3.71	0.06	-
8	40.67±4.22	38.5±6	37±3.77	0.22	-
16	37.5±-	42.67±7.52	32.5±3.53	0.27	-
24	1(2.5)	6(15)	2(5)	0.08	-
Total instant analgesic tramadol amount (mg)					
0	45±0	40±-	39.71±13.21	0.86	-
1	39.77±3.94	42.5±14.39	47.65±19.54	0.39	-
4	55.47±19.81	41.13±11.16	65.33±26.04	0.003	0.11 0.27 0.002
8	77.97±31.31	55.57±19.38	71.78±34.96	0.04	0.04 0.76 0.14
16	80±36.14	61.5±27.38	74.19±35.93	0.18	-
24	19(47.5)	23(57.5)	27(67.5)	0.20	-

*One-Way ANOVA test, ** Post Hoc test-Tukey; $p<0.05$ is significant. SD: Standard deviation.

The difference in VAS between the groups was significant at 0 ($p^*=0.005<0.05$ and $p^*=0.001<0.05$, respectively) and 24 hours in both sitting ($p^*=0.005<0.05$ and $p^*=0.005<0.05$, respectively) and supine ($p^*=0.001<0.05$ and $p^*=0.001<0.05$, respectively) positions. There were no significant differences at other follow-up hours. The difference between the satisfaction scale rank order totals was significant ($p^*=0.02<0.05$; $p^{**}=0.009<0.05$) (Table 4).

Table 4. Assessment of visual analog score and satisfaction scale between treatment groups (n=120).

	Bupivacaine (n=40)	Bupivacaine +Dexmedetomidin (n=40)	Bupivacaine +Dexametazon (n=40)		
Hour	Mean±SD	Mean±SD	Mean±SD	p value*	p value** 1 vs 2, 1 vs 3, 2 vs 3
VAS sitting position					
0	0(0-0) 0.05±0.32	0(0-0) 0.15±0.48	0(0-2) 0.85±1.61	0.005	0.89 0.001 0.005
1	0.5(0-2) 1.03±1.21	0(0-1) 0.7±1.04	0(0-2) 1.38±1.76	0.33	-
4	2(1-3) 2.28±1.37	2(1-2) 2.32±1.47	2(1-3) 2.42±1.75	0.95 0.19	- -
8	2.5(2-3) 3.02±1.38	2(2-3) 2.57±1.01	2(1-3) 2.85±1.65		
16	2(2-3) 2.88±1.24	2(2-3) 2.83±1.1	2(0.25-3) 2.25±1.48	0.14	-
24	2(2-3) 2.3±0.68	2(2-3) 2.57±1.01	1(1-3) 1.7±1.2	0.005	0.45 0.03 0.001
VAS supine position					
0	0(0-0) 0.05±0.32	0(0-0) 0.15±0.48	0(0-0) 0.85±1.36	0.001	0.86 0.001 0.001
1	1(0-2)	0(0-1)	0(0-3.75)	0.29	-

	0.85±0.97	0.63±0.89	1.13±1.32		
	2(1-3)	2(1-3)	2(1-4)		
4	2.07±1.22	1.78±1.12	1.98±1.32	0.47	-
	3(2-4)	3(2-3)	3(2-4)		
8	2.38±1.03	2.18±0.87	2.1±1.23	0.43	-
	3(2-4)	3(2-4)	2(1-3.75)		
16	2.25±0.83	2.25±0.92	1.73±1.03	0.1	-
	2(2-3)	3(2-3)	2(1-3.5)		
24	2.2±0.72	2.28±0.78	1.43±1.05	0.001	0.92 0.001 0.001
	3(2-3)	3(3-4)	3(3-4)		
Satisfaction Scale	2.73±0.98	3.05±0.78	3.3±0.79	0.02	0.21 0.009 0.39

*Kruskal-Wallis H test, ** Post Hoc test-Tukey; p<0.05 is significant. Q1-Q3: 25%-75%. SD: Standard deviation, VAS: Visual Analogue Score.

4. Discussion

Local anesthesia is widely used for the comfort of the patient in the postoperative period [8]. Caesarean section is one of the major surgical procedures and, as expected, there is significant postoperative discomfort and pain [19]. By postoperative analgesia in the post-cesarean period, it is difficult to achieve balance in terms of ensuring the comfort of the mother on the one hand, and avoiding any negative effects on the newborn on the other hand [9]. In this context, although opioids provide good analgesia, they have undesirable side effects such as nausea, vomiting and dizziness that reduce overall patient satisfaction [19,20]. Hence, various drugs or techniques such as non-opioids, adjuvants and TAP blockade have been used to reduce perioperative opioid consumption and thus its adverse effects [21]. In a study conducted by McDonnell et al., a more than 70% reduction in morphine requirement and a longer time to the first patient-controlled analgesia (PCA) morphine request were observed in pregnant women in the group in which the TAP block was applied with ropivacaine, compared to the placebo block. Postoperative VAS pain scores at rest and during movement were reduced after TAP block [19].

The risk of complications associated with the TAP block is unknown [9]. An ideal local anesthetic is also expected to provide complete sensory blockade and have an optimal duration of action. Of the two commonly used local anesthetics, for example, bupivacaine has a significantly longer duration of action than lidocaine and ropivacaine [14,22].

Recently, it has been shown that supplementing TAP block application with some adjuvants such as dexmedetomidine and dexamethasone reduces pain scores and the need for additional analgesics, and therefore their associated side effects [9]. The addition of dexmedetomidine, a highly selective central alpha-2 adrenergic agonist, to bupivacaine in the TAP block has been used in various studies [4,15,16,21,23]. This combination provided a longer postoperative pain-free period and better analgesia compared to bupivacaine alone, as well as reduced the need for rescue analgesics [21]. Ramya et al. reported in their study that the block duration was 14 hours in the bupivacaine + dexmedetomidine TAP block and 8 hours in the bupivacaine TAP block alone [16]. In the study of Shehab et al., the amount of morphine consumption in the first 24 hours was found to be 24.3 in the bupivacaine + dexmedetomidine TAP block mg and 11 mg in the bupivacaine TAP block alone [24].

Like dexmedetomidine, several researchers have used dexamethasone, a corticosteroid, as a supplemental to bupivacaine in the TAP block [1,4,25]. In a study by Sachdeva et al. [1], the time needed to first analgesic was significantly longer in the dexamethasone + ropivacaine combination group compared to the ropivacaine alone group (5.92 vs. 3.11 hours). Additionally, a significant decrease in tramadol requirement was observed in the postoperative period (100 mg vs 140 mg). Patient satisfaction with pain relief was also greater (57.14% vs 25.71%). They also observed significant reductions in nausea and vomiting rates (8.57% vs 2.86% and 8.57% vs 0%, respectively).

Various mechanisms have been proposed to explain the analgesic effect of corticosteroids. One of these mechanisms is that steroids suppress the synthesis and secretion of various inflammatory mediators, which prolongs the duration of analgesia up to 48 hours. Another assumption is its direct effect on the nerve membrane. It has also been suggested that steroids cause some degree of

vasoconstriction, reducing local anesthetic absorption and ultimately prolonging the duration of analgesia [1].

In many studies, it has been reported that supplemental TAP block applications provide a faster onset of effect and a longer duration of analgesia, reduce the need for postoperative morphine, and reduce the incidence of nausea and vomiting, without any significant side effects. Additionally, increases are observed in VAS score and patient satisfaction scale [1,4,9,14-16,21,23,25]. In a study by Singla et al, the addition of dexmedetomidine to ropivacaine in the TAP block significantly reduced initial postoperative pain and prolonged the time needed to first analgesic with minimal side effects compared to dexamethasone [4].

Surprisingly, the findings observed in our study were inconsistent with the results of other studies. The possible reason for this may be that BMI is higher in Group B (bupivacaine) than in Group BD (bupivacaine + dexmedetomidine) and Group BDx (bupivacaine + dexamethasone), which is a factor that may affect the result. Unlike many other studies, in our study, the mean BMI was higher in the group given only bupivacaine as a result of randomization. In fact, as BMI increases, there are fewer sensory nerves per unit volume and the pain threshold increases [26]. In addition, due to the decrease in vascularity per unit volume, analgesic absorption slows down, and both the pain threshold increases, and the duration of analgesia get longer [1]. In Group B, the operation time was also significantly longer than in the other two groups.

A consensus needs to be reached on the safe dose and concentration of local anesthetic solution to limit systemic toxic complications of TAP block without affecting its analgesic effectiveness [9].

5. Conclusions

TAP block significantly reduces pain after cesarean section, prolongs the time to first analgesic request, and reduces the need for additional opioid analgesics. The addition of an adjuvant to the anesthetic used in the TAP block significantly improves these positive effects without a significant increase in side effects. However, these results may be significantly affected depending on the type of analgesic and adjunct used, their dosage, and patient factors such as body mass index, which we suggested in our study. In this regard, comprehensive, standardized, randomized controlled studies are needed.

Author Contributions: S.U. and O.K. conceptualized and designed the study; S.U., O.K. AND S.H. collected the original data; S.U. and O.K. analyzed the data; S.U., O.K. and S.T. interpreted the analysis; S.U. and O.K. prepared the original draft; S.U., O.K., S.H. and S.T. reviewed and edited the draft, and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Clinical Research Ethics Committee of Hatay Mustafa Kemal University (meeting date: 20.02.2020, decision no: 05)

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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