ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

Original Research Article

"A comparative study on Efficacy and safety of transdermal fentanyl patch with placebo patch on postoperative pain relief after caesarean section"

Dr. Jaggannagari Chandupatla Varun Reddy[1], Dr. Kokkireni Sashi Bindu[2], *Dr. Dillly Nitish Chandra[3], Dr. S. Samanth Reddy[4]

1. 2. 3. Post Graduate, Department of Anaesthesia, Kamineni Academy of Medical Sciences and Research Centre, L. B. Nagar, Hyderabad.

4. Assistant Professor, Department of Anaesthesia, Kamineni Academy of Medical Sciences and Research Centre, L. B. Nagar, Hyderabad.

***Corresponding Author: Dr. Dillly Nitish Chandra, Post Graduate, Department of Anaesthesia, Kamineni Academy of Medical Sciences and Research Centre, L. B. Nagar, Hyderabad.**

ABSTRACT:

Background: Management of postoperative pain in Lower segmental caesarean section(LSCS) parturient is a lot to be desired. It is advocated that the pain management has to be for 48 hours after lower abdominal surgery.

OBJECTIVES: To determine the safety and effectiveness of a transdermal fentanyl delivery system for the relief of post-operative pain using fentanyl patches (duragesic) 50 microgram. hour following elective caesarean section and to observe sedation scores and to note side effects, if any.

MATERIAL & METHODS: Study Design: Prospective randomized controlled study. **Study area:** Department of Anaesthesia, Kamineni Academy of Medical Sciences and Research Centre, L. B. Nagar, Hyderabad. **Sample size:** Study consisted a total of 70 cases. Prospective, randomized, 2-arm study on 70 patients was randomly allocated to two groups of 35 each: Group A: Patients who received transdermal therapeutic system-fentanyl 50 µg/hour. Group B: Patients who received transdermal placebo patch **Sampling method:** Simple Random sampling method. Pain was assessed post-operatively at 3^{rd}, 7^{th}, 11^{th}, 15^{th}, 19^{th}, 23^{rd}, 27^{th}, 31^{st}, 35^{th}, 39^{th}, 43^{rd}, 47^{th}, 48^{th} hours using a visual analogue scale (VAS). Where '0' is no pain, 10 is worst pain imaginable, in between 0 & 10, where 1-3 denotes mild pain, 3-6 denotes moderate pain, 6-9 denotes severe pain. If the VAS during any time study was more (or) equal to five injection tramadol 100 mg intravenously was administered intra-venous as rescue analgesia. Time at which rescue analgesia administered to each group and side effects with the use of study drug were also noted.

Results: In 48^{th} postoperative hour, all the patients in group A had a VAS score of 0 and in group B, 31 patients had a VAS score of 1-3 and 4 patients had a VAS score of 4-6. Hence, it showed a P value of <0.001 which was found to be statistically significant.

CONCLUSION: After completing the study, we conclude that transdermal administration of fentanyl 50 µg/h preoperatively is an effective noninvasive and convenient technique for postoperative pain relief after elective caesarian section surgery and allows delivery of a potent analgesic agent with acceptable minimal side effects, better quality of life and better patient acceptability.

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

Keywords: post-operative pain, Fentanyl, transdermal therapeutic system(TTS)

INTRODUCTION:

Although post-operative pain is arguably the most common clinical problem in our hospitals, it is often dismissed with an order for intermittent intramuscular opiate injections to be given at the discretion of an overworked nursing staff. This generally results in patients waiting for pain relief, then a period of relief and perhaps drowsiness, and the cycle is repeated. With this method, pain relief is only satisfactory (Adequate relief without unwanted sedation) for about one third of the time. Good postoperative analgesic management probably carries benefits other than increased patient comfort. The magnitude of the neuro endocrine stress response, postoperative pulmonary complications and the incidence of myocardial ischemia can be decreased. Early mobilization can be achieved and the patient can be discharged from the hospital sooner.[1]

Management of postoperative pain in Lower segmental caesarean section (LSCS) parturient is a lot to be desired. It is advocated that the pain management has to be for 48 hours after lower abdominal surgery.

Fentanyl is a synthetic opioid with short acting analgesic activity after intravenous or subcutaneous administration. The low molecular weight, high potency and lipid solubility of fentanyl make it suitable for delivery via the transdermal therapeutic system (TTS). These systems are designed to release the drug in to skin at a constant rate ranging from 25 to100 micrograms/hr, multiple systems can be applied to achieve delivery rates. Initially, much of the clinical experience with fentanyl TTS was obtained. In patients with acute postoperative pain.[2]

Compared with other opioids, fentanyl patches have been associated with better pain relief, less constipation, lesser incidence of vomiting, good patient accessibility and they enhance the quality of life.

Pain management postpartum is complicated by concerns regarding exposure of the neonate through breastfeeding as well as increased risk of maternal thromboembolism and interference with lactation from sedation. The American academy of pediatrics considers fentanyl use compatible with breastfeeding based on short-term maternal use. Fentanyl levels measured in both breast milk and baby's serum were low [3].

The way for improving postoperative pain management should include procedure specific guidelines, new methods to predict postoperative pain and new drugs and delivery systems [4].

Hence, objective of this study was to determine the safety and effectiveness of a transdermal fentanyl delivery system for the relief of postoperative pain using fentanyl patches (duragesic) 50 microgram/hour following elective caesarean section.

OBJECTIVES:

To determine the safety and effectiveness of a transdermal fentanyl delivery system for the relief of post-operative pain using fentanyl patches (duragesic) 50 microgram./ hour following elective caesarean section and To observe sedation scores and To note side effects, if any.

MATERIAL & METHODS:

Study Design: Prospective randomized controlled study.

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

Study area: Department of Anaesthesia, Kamineni Academy of Medical Sciences and Research Centre, L. B. Nagar, Hyderabad.
Study Period: March 2022 – August 2022 (6 months).
Study population: Female patients posted for elective cesarean section in the department of Anesthesia.
Sample size: Study consisted a total of 70 cases.
Prospective, randomized, 2-arm study on 70 patients was randomly allocated to two groups of 35 each:
Group A: Patients who received transdermal therapeutic system-fentanyl 50 mg/hour.
Group B: Patients who received transdermal placebo patch
Sampling method: Simple Random sampling method.
Inclusion criteria:
• Female patients aged between 18-45 years
• ASA I – II
• Body mass index (BMI) between 20-25 kg/m2
• Scheduled for elective Caesarean surgeries
Exclusion criteria:
• Patients who have received opioids pre-operatively
• Contraindication to regional block (coagulation defect, local infection at the site of injection or patient refusal)
• Patients having moderate or severe renal and hepatic impairment
• Patients with documented history of opioid sensitivity or drug abuse
Ethical consideration: Institutional Ethical committee permission was taken prior to the commencement of the study.

Study tools and Data collection procedure:
Detailed pre-anesthetic check-up including anticipation of difficult airway was done and patients were counseled regarding sub-arachnoid block (procedure, risks and benefits) and visual analogue scale which is a line graded from 0-10, where 0=no pain and 10=the worst pain imaginable. Patients were pre-mediated with Inj omeprazole 40mg night before and morning of surgery, Inj Ranitidine 50mg i.v. and Inj Metoclopramide 10mg iv, 5 mins prior to surgery. On the day of surgery, before shifting to the operation theatre, an 18-gauge peripheral venous cannula was inserted and patients were preloaded with 500ml of ringer lactate. In the pre-operative room, baseline readings of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation were measured. Consent was checked. Monitors such as Non-invasive blood pressure with right sized BP cuff, pulse oximetry, capnography, functional suction tubing, Electrocardiography, were connected.
Pain was assessed post-operatively at 3^{rd}, 7^{th}, 11^{th}, 15^{th}, 19^{th}, 23^{rd}, 27^{th}, 31^{st}, 35^{th}, 39^{th}, 43^{rd}, 47^{th}, 48^{th} hours using a visual analogue scale (VAS). Where ‘0’ is no pain, 10 is worst pain imaginable, in between 0 & 10, where 1-3 denotes mild pain, 3-6 denotes moderate pain, 6-9 denotes severe pain. If the VAS during any time study was more (or) equal to five injection tramadol 100 mg intravenously was administered intra-vinous as rescue analgesia. Time at

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

which rescue analgesia administered to each group and side effects with the use of study drug were also noted.

Patient was monitored for sedation using Ramsay sedation score (RSS), by this patient were categorized in to 2 groups where group – 1 is asleep and group – 2 is awake for 4 hours. Patient monitored for any side effects of fentanyl like constipation, respiratory depression, nausea**,** vomiting. If vomiting present ondonsetron 4mg, intravenous was given.

STATISTICAL METHODS:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and result on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Student 1 test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

OBSERVATIONS & RESULTS:

Table 1: Age distribution of patients

Age in years	**Group A**	**Group B**	**Total**
<20	1 (2.9%)	0 (0%)	1 (1.4%)
20-30	32 (91.4%)	32 (91.4%)	64 (91.4%)
31-40	2 (5.7%)	3 (8.6%)	4 (5.7%)
Total	35 (100%)	35 (100%)	70 (100%)
Mean ± SD	25.40 ± 3.73	25.51 ± 3.31	25.46 ± 3.50

70 patients were randomized into two groups A and B of 35 patients each. The mean age in group A was 25.40±3.73 years as against 25.51±3.31 years in group B. This was found to be statistically insignificant (P value = 0.893).

Table 2: Duration of Surgery

Duration of Surgery	**Group A**	**Group B**	**Total**
1-30	2 (5.7%)	3 (8.6%)	5 (7.1%)
31-60	33 (94.3%)	32 (91.4%)	65 (92.9%)
Total	35 (100%)	35 (100%)	70 (100%)
Mean ± SD	40.29 ± 6.29	38.71 ± 4.08	39.50 ± 5.33

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

P = 0.220, Not significant, student t test

The mean duration of surgery was 40.29±6.29 min in group A as against 38.71±4.08 min in group B. Average duration of surgery for both groups was 30-45 minutes. This was found to be statistically insignificant.

Table 3: Pain score in two groups of patients

Pain score	Group A (n=35)	Group B (n=35)	Total	P value
3rd hour				
* 0	26(74.3%)	0(0%)	26(37.1%)	<0.001**
* 1-3	9(25.7%)	15(42.9%)	24(34.3%)	
* 4-6	0(0%)	20(57.1%)	20(28.6%)	
* 7-10	0(0%)	0(0%)	0(0%)	
7th hour				
* 0	5(14.3%)	0(0%)	5(7.1%)	<0.001**
* 1-3	23(65.7%)	14(40%)	37(52.9%)	
* 4-6	7(20%)	21(60%)	28(40%)	
* 7-10	0(0%)	0(0%)	0(0%)	
11th hour				
* 0	10(28.57%)	0(0%)	10(14.28%)	<0.001**
* 1-3	19(54.28%)	24(68.57%)	43(61.42%)	
* 4-6	6(17.14%)	11(31.42%)	17(24.28%)	
* 7-10	0(0%)	0(0%)	0(0%)	
15th hour				
* 0	9(25.7%)	0(0%)	9(12.9%)	<0.001**
* 1-3	24(68.57%)	27(77.14%)	51(72.85%)	
* 4-6	2(5.71%)	8(22.85%)	10(14.28%)	
* 7-10	0(0%)	0(0%)	0(0%)	
19th hour				
* 0	8(22.9%)	0(0%)	8(11.4%)	<0.001**
* 1-3	27(77.1%)	27(77.1%)	54(77.14%)	
* 4-6	0(0%)	8(22.9%)	8(11.42%)	
* 7-10	0(0%)	0(0%)	0(0%)	
23rd hour				
* 0	9(25.7%)	0(0%)	9(12.9%)	<0.001**
* 1-3	24(68.57%)	29(82.85%)	53(75.71%)	
* 4-6	2(5.71%)	6(17.14%)	8(11.42%)	
* 7-10	0(0%)	0(0%)	0(0%)	
27th hour				
* 0	17(48.6%)	0(0%)	17(24.3%)	<0.001**
* 1-3	15(42.85%)	25(71.42%)	40(57.14%)	
* 4-6	3(8.571%)	10(28.57%)	13(18.57%)	
* 7-10	0(0%)	0(0%)	0(0%)	
31ST Hour				

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

* 0	27(77.1%)	0(0%)	27(38.6%)	<0.001**
* 1-3	7(20%)	35(100%)	42(60%)	
* 4-6	0(0%)	0(0%)	0(0%)	
* 7-10	0(0%)	0(0%)	0(0%)	
35th hour				
* 0	29(82.9%)	0(0%)	29(41.4%)	<0.001**
* 1-3	6(17.1%)	31(88.57%)	37(52.85%)	
* 4-6	0(0%)	4(11.42%)	4(5.71%)	
* 7-10	0(0%)	0(0%)	0(0%)	
39th hour				
* 0	28(80%)	0(0%)	28(40%)	<0.001**
* 1-3	5(14.3%)	30(85.71%)	35(50%)	
* 4-6	2(5.71%)	5(14.28%)	7(20%)	
* 7-10	0(0%)	0(0%)	0(0%)	
43rd hour				
* 0	32(91.4%)	0(0%)	32(45.7%)	<0.001**
* 1-3	2(5.7%)	32(91.42%)	34(48.57%)	
* 4-6	0(0%)	3(8.57%)	3(4.28%)	
* 7-10	0(0%)	0(0%)	0(0%)	
47th hour				
* 0	33(94.3%)	0(0%)	35(47.1%)	<0.001**
* 1-3	2(5.7%)	35(100%)	37(52.9%)	
* 4-6	0(0%)	0(0%)	20(28.6%)	
* 7-10	0(0%)	0(0%)	0(0%)	
48th hour				
* 0	35(100%)	0(0%)	35(50%)	<0.001**
* 1-3	0(0%)	31(88.57%)	31(44.28%)	
* 4-6	0(0%)	4(11.42%)	4(5.71%)	
* 7-10	0(0%)	0(0%)	0(0%)	

In 48th postoperative hour, all the patients in group A had a VAS score of 0 and in group B, 31 patients had a VAS score of 1-3 and 4 patients had a VAS score of 4-6. Hence, it showed a P value of <0.001 which was found to be statistically significant.

Table 4: Comparison of Pain Score in two groups of patients

Pain score	Group A	Group B	P value
3rd hour	0.37±0.69	3.91±1.72	<0.001**
7th hour	2.23±1.55	2.97±1.32	0.035*
11th hour	1.31±1.41	2.69±0.76	0.012*
15th hour	1.03±0.89	2.63±0.49	0.001**
19th hour	0.97±0.66	2.20±0.00	0.012*
23rd hour	0.83±0.57	2.91±0.32	0.012*

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

27th hour	0.51±0.51	2.01±0.32	<0.001**
31st hour	0.24±0.50	1.98±0.30	<0.001**
35th hour	0.17±0.38	2.00±0.32	<0.001**
39th hour	0.14±0.36	2.10±0.00	<0.001**
43rd hour	0.06±0.24	2.13±0.20	<0.001**
47th hour	0.06±0.24	1.70±0.00	<0.001**
48th hour	0.00±0.00	1.92±0.03	<0.001**

Table 5: Rescue Analgesia requirement between groups

Rescue Analgesia	Group A	Group B	P Value
3rd hour	10	33	<0.001
7th hour	6	21	<0.001
11th hour	6	11	<0.001
15th hour	2	8	<0.001
19th hour	0	8	<0.001
23rd hour	2	6	<0.001
27th hour	3	10	<0.001
31st hour	0	0	
35th hour	0	4	<0.001
39th hour	2	5	0.012
43rd hour	0	3	<0.001
47th hour	0	0	
48th hour	0	4	<0.001

Table 6: Ramsay Sedation score in two groups of patients

Ramsay Sedation Score	Group A No. of patients	Group B No. of patients	Total
1	15(42.85%)	20(57.14%)	35(50%)
2	20(57.14%)	15(42.85%)	35(50%)
Total	35(100%)	35(100%)	70(100%)

P=1.000, Not significant, Fisher Exact test

Ramsay sedation score was checked 3 hours postoperatively in both the groups and the patients had a score of 1-2 which was found to be statistically insignificant.

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

Table 7: Side effects in two groups of patients

Side Effects	Group A (n=35)	Group B (n=35)	Total (n=70)	P Value
Nausea				
• Negative	31(88.57%)	35(100%)	66(94.28%)	P<0.05
• Positive	4(11.42%)	0(0%)	4(5.714%)	
Vomiting				
• Negative	33(94.28%)	34(97.14%)	67(95.71%)	1.000
• Positive	2(5.71%)	1(2.85%)	3(4.28%)	
Itching				
• Negative	35(100%)	35(100%)	70(100%)	1.000
• Positive	0(0%)	0(0%)	0(0%)	
Erytherna				
• Negative	35(100%)	35(100%)	70(100%)	1.000
• Positive	0(0%)	0(0%)	0(0%)	
Respiratory depression				
• Negative	35(100%)	35(100%)	70(100%)	1.000
• Positive	0(0%)	0(0%)	0(0%)	
Any other side effects				

Nausea and Vomiting were observed in group A patients receiving transdermal fentanyl compared to group B. in group A, 11.42% of the patients had nausea and 5.71% of patients had vomiting whereas in Group B,2.85% of patients had vomiting which was found to be metochlopromide 10 mg intravenously.

DISCUSSION:

Although control of postoperative pain is important for recovery, clinical surveys continue to show that many patients experienced moderate to severe degrees of pain following surgery. McCaffery and Ferrell showed that over 50% of surgical patients experienced inadequate pain relief following surgery with negative physiological and psychological consequences[5]. Administration of fentanyl by the transdermal route is appealing because fentanyl is a potent agent with well- defined clinical pharmacological characteristics. Transdermal fentanyl has been demonstrated to provide effective analgesia for acute post-operative pain.

Our study and control groups were both comparable demographically. Duration of surgery was comparable between the two groups. In the present study, the mean age in group A was 25.40±3.73 years as against 25.51±3.31 years in group B. this was found to be statistically insignificant (P value = 0.893).

In our study, there was a significant decrease in pain in Group A than compared to Group B which was statistically significant. We are in agreement with Sandler et al's study. Sandler et al, in their study found that Transdermal fentanyl 50mcg/hr provided effective analgesia for acute postoperative pain. The VAS pain score were consistently better in the fentanyl group

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

compared with the placebo group, and these lower pain scores were strongly correlated with serum fentanyl concentrations [6].

Barrera et al, which assessed the safety and efficacy of transdermal fentanyl used as main postoperative analgesic in patients undergoing dorsal or lumbar spine fusion by comparing the TDF, 50 µg/h, with placebo. VAS scores and rescue analgesic requirements were lower in transdermal fentanyl group ($p<0.05$) [7].

Our study is also consistent with the study done by Samy et al, where pain assessment was done throughout the period of the study (48 hours) by using the VAS score. When comparing the two groups together at the same time, it was found that the VAS was significantly lower in the TDF group compared to the control group[4].

In the present study, there was a significant difference in the requirement of rescue analgesia. As compared to Group A which received TDF 50mcg/hr. Group B patients required more rescue analgesia with a P value of <0.001. we are in agreement with Sevarino et al and Sandler et al.s study. **Sevarino et al.** compared TDF in two different delivery rates 25µg/h and 50 µg/h with placebo for postoperative analgesia after abdominal gynecologic surgery (the patches were applied one hour before surgery and removed after 72 hours). They found that there were no differences in the pain intensity in both TDF groups and no differences in rescue analgesia in the TDF group with delivery rate 25 µg/h when compared with the placebo group. There was a significant reduction in the rescue analgesia in the TDF group with a delivery rate of 50 µg/h [8].

In the present study, 11.42% of patients who received TDF 50mcg/hr had nausea and 5.71% of patients had vomiting compared to the control group, where 2.85% of patients had vomiting. Minville et al. , reported that in the TDF group (Duragesic 50 mcg/hr) there were no reported cases of sedation, respiratory depression or erythema. Pruritus occurred in one patient and nausea / vomiting occurred in 7 patients. The only prominent adverse event was the occurrence of local erythema in 30% of patients received transdermal fentanyl. The transdermal fentanyl group had more pruritus and nausea ($p<0.02$)[9]. In Samy et al [4]study, Nausea occurred in (33.3%) of patients in the TDF group, which is different from our study where no any case of erythema was reported, and no respiratory depression were observed.

Overall sedation scores were not increased by transdermal fentanyl. Higher rescue analgesia usage in the placebo and lower rate fentanyl administration groups may account for this. In our study, patients were distinctly informed about the procedure and possible side effects, thus monitoring of each patient was organized in agreement with family member. In very few cases, nausea was reported, especially when patients were moving, which was stopped at moment of siting. Other side effects were not reported.

CONCLUSION:

After completing the study, we conclude that transdermal administration of fentanyl 50 µg/h preoperatively is an effective noninvasive and convenient technique for postoperative pain relief after elective caesarian section surgery and allows delivery of a potent analgesic agent with acceptable minimal side effects, better quality of life and better patient acceptability.

REFERENCES:

1. Thomas A, Torda “Postoperative analgesia” Aust presser 1995: 18: 88-91

ISSN:0975-3583,0976-2833 VOL13, ISSUE 08, 2022

2. Jeat W, Besfield P "Transdermal fentanyl A review of its pharmacological properties and therapeutic efficacy in pain control", 1997 Jan, 53(1): 109-38.
3. Cohen RS, Fentanyl transdermal analgesia during pregnancy and lactation. Journal of Human Lactation 2009 Aug 1: 25(3): 359-61.
4. Samy A, Amr, Mostafa G, Mostafa, and Mohamed A.M, Mostafa "Efficacy and safety Transdermal Fentanyl patches on postoperative pain relief after major abdominal surgery" Journal of Americal Science 2012:8(6).
5. McCaffrey M, Ferrell BR, Nurses' knowledge of pain assessment and management: How much progress have we made?. Journal of pain and symptom management. 1997 Sep 30: 14():175-88.
6. Sandler AN, Baxter A, Katz J, Norman P, Koren G, Roger S, Hull K, Samson B, Friedlander M, klein J. A double-blind, placebo-controlled trial of transdermal fentanyl after abdominal hysterectomy analgesic, respiratory, and pharmacokinetic effects.1994.
7. Barrera E, Fernandez - Galinski S, Ferrer MD, Escolano F, Puig M, 662 postoperative analgesia induced by transdermal fentanyl in dorsal and lumbar spine arthrodesis. European Journal of pain. 2009 Sep 30: 13:S191-2.
8. Sevarino Fb, Naulty JS, Sinatra R, Chin ML, Paige D, Conry K, Silverman DG. Transdermal fentanyl for postoperative pain management in patients recovering from abdominal gynecolohic surgery. Anaesthesiology. 1992 Sep: 77(3):463-6.
9. Minville V, Lubrano V, Bounes V, Pianezza A, Rabinowitz A, Gris C, samii K, Fourcade O. postoperative analgesia after total hip arthroplasty: patient controlled analgesia versus transdermal fentanyl patch, Journal of clinical anaesthesia. 2008 Jun 30: 20(4):280-3.
10. Joseph CC, Singh DR, Jaya V, Ravishankar M. Efficacy of Transdermal Fentanyl Patches In Acute Post Operative Pain Relief: A Randomised Double Blinded Placebo Controlled Trial. Medical Science. 2015 Jan;4(1).
11. Choi JH, Kang HD, Park JH, Gu BS, Jung SK, Oh SH. The efficacy of fentanyl transdermal patch as the first-line medicine for the conservative treatment of osteoporotic compression fracture. Korean J Neurotrauma. 2017;13:130–136
12. Jang JS, Hwang SM, Kwon Y, Tark H, Kim YJ, Ryu BY, Lee JJ. Is the transdermal fentanyl patch an efficient way to achieve acute postoperative pain control?: A randomized controlled trial. Medicine. 2018 Dec;97(51).