

ORIGINAL RESEARCH

OBSTETRIC ANESTHESIA

Targeting G-protein coupled receptors in the spinal dorsal horn for prevention of shoulder tip pain with cesarean section; a myth or a fact

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ABSTRACT

Background & objective: Shoulder tip pain (STP) is a commonly observed, annoying and mostly neglected consequence of cesarean section and little is known as well as explored about intraoperative shoulder pain. We studied the effectiveness of activation of G protein-coupled receptors (GPCRs), by adding intrathecal fentanyl to the spinal anesthesia as a preventive analgesia for shoulder pain with cesarean section (CS).

Methodology: A total of 44 parturients undergoing elective CS were divided into two equal groups; Group F patients received 2.5 ml of hyperbaric bupivacaine 0.5 % and 25 µg fentanyl. Group C (control group) patients received 2.5 ml of hyperbaric bupivacaine 0.5. The incidence and severity of intraoperative STP was noted. The severity of that pain was assessed using the verbal numerical rating scale (0-10) at the time of complaint. The STP was monitored every 2 h for 8 h postoperatively.

Results: There was no statistical difference in the incidence and severity of STP in both groups. The average for diastolic blood pressure was 74 ± 6.5 mmHg in Group C vs 72 ± 8.5 mmHg in Group F and the average for the heart rate was 84 ± 6 bpm vs 79 ± 12 bpm in Group C and F respectively. Point biserial correlation revealed a positive correlation (0.3) between t STP and total blood loss; however, this correlation wasn't statistically significant ($P = 0.06$).

Conclusion: Activation of G protein linked receptor by adding fentanyl to the local anesthetic for spinal anesthesia decrease the incidence of shoulder tip pain; however, the difference is statistically insignificant.

Abbreviations: CS - cesarean section; GPCR - G protein-coupled receptor; STP - Shoulder tip pain

Keywords: Anesthesia, spinal; Cesarean section; Pain; Pain, postoperative; Pain, shoulder tip; fentanyl; G protein-coupled receptors.

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1. INTRODUCTION

The most common surgery performed on women around the world is cesarean section (CS). The majority of caesarean sections these days are carried out under regional analgesia, though some need to be carried out

under general anesthesia, particularly in emergency situations or when there is a contraindication to the use of regional anesthesia. Benefits of spinal anesthesia (SA) include an awake mother at birth, minimizing or avoiding the risk of general anesthesia (aspiration, difficulty intubation, etc.) and minimal side effects to the newborn.¹

Shoulder tip pain (STP) is a usual complication after laparoscopy with the reported incidence varying between 35% to 80%.² Recent studies suggest that this type of pain is also seen after CS under SA. Little is known or studied regarding the pathogenesis of STP.³

STP, in some patients, can be more excruciating than the pain from the surgical incision. This pain may be associated with diaphragmatic irritation/injury from local acidosis, the irritating effects of carbon dioxide during pneumoperitoneum, or stretching forces on the diaphragm. Although carbon dioxide is not used in CS, compared to laparoscopic surgeries, stretching forces on the diaphragm during CS can be one of the causes of STP in these patients.⁴

It is believed that accumulation of blood or amniotic fluid during CS into the subdiaphragmatic space may be the cause of STP.⁵ Retained blood clots in patients undergoing CS can induce diaphragmatic discomfort and stimulate the phrenic nerve. Peritoneal cleaning and visceral manipulation may also play a part.⁶

Fentanyl is a commonly used lipophilic opioid for SA and approved as an intraoperative anti-nociceptor.⁷ Intrathecal opioids bind to G-protein coupled synaptic receptors (GPCRs) in laminae I and II of the dorsal horn. Activation of the receptors cause potassium channel opening and calcium channel closure, this reduces the release of glutamate and substance P with reduction of nociceptive transmission. Opioids may also reach the brain stem through the posterior radicular artery.⁸

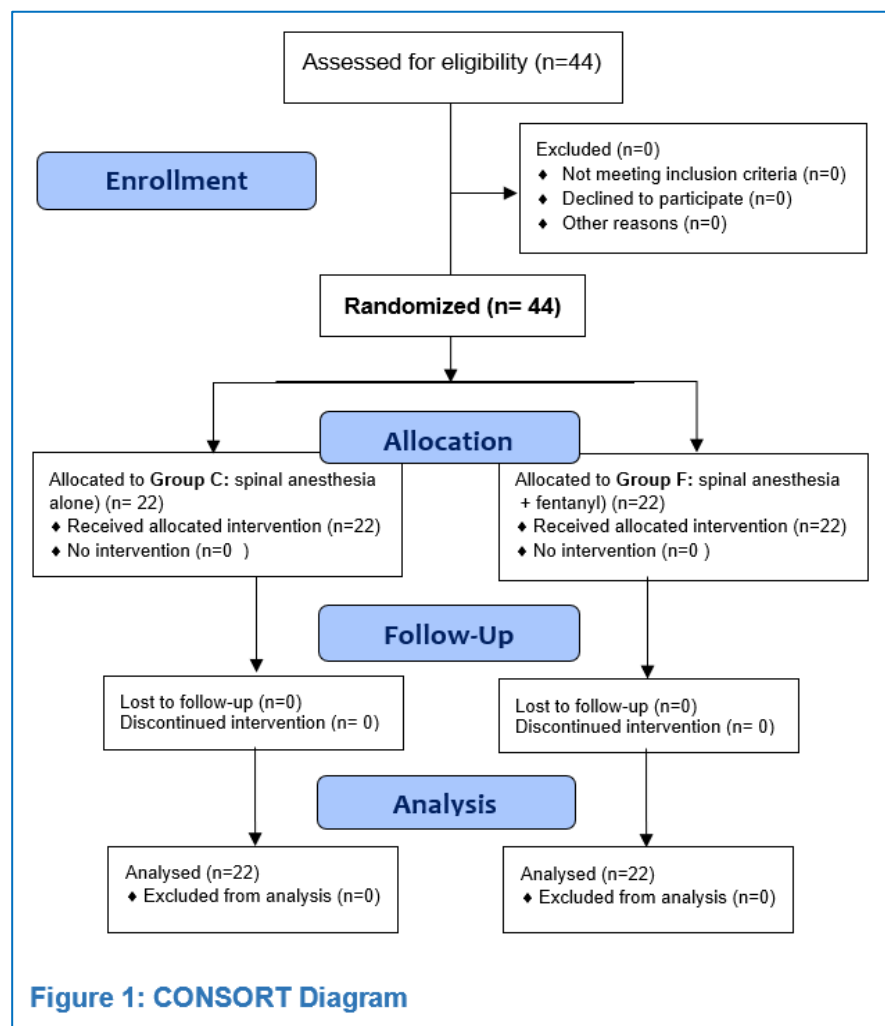
The aim of the study was to test the effectiveness of activation of GPCRs in the dorsal horn of the spinal cord using intrathecal fentanyl with spinal bupivacaine in the prevention of STP associated with CS. The primary outcome was to study the incidence and the severity of STP and analgesic consumption among the two groups. Secondary outcome was to study the effect of addition of intrathecal fentanyl on the hemodynamic parameters of the parturients.

2. METHODOLOGY

A six-month prospective observational study was conducted at Ain Shams University Obstetric Hospital, from March 01, 2023 to August 01, 2023. All procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments, as well as the Ain Shams University Hospital Ethics Committee (FMASU R 213 / 2022, dated November 24, 2022). The trial was registered with Trial registration and ethical approval: clinical trials (www.clinicaltrials.gov) database ID no (NCT05730751).

2.1. Randomization and patient allocation

The study included parturients, aged from 18-45 y, ASA physical status II-III, with uncomplicated, singleton pregnancies of at least 36 weeks gestation. Parturient with cardiac, liver, or renal disease, allergic to amide local anesthetics were excluded. Parturients with a history of epilepsy or any other neurological problem,



any contraindication of regional anesthesia, or patient refusal and intrauterine growth restriction or fetal compromise, were also excluded.

PASS 15 program was used for sample size calculation; setting power at 80% and alpha error at 0.05, it was estimated that a sample size of 22 women per group would be needed to detect the difference between two groups regarding prevention of shoulder tip pain assuming that proportion of women without shoulder pain in Group F = 57.5% and in Group C = 22.5% (Hamed and Elsayy, 2021). The patients were randomly divided into two equal groups Group F and Group C. Randomization was done by computer-generated number lists and using opaque sealed envelopes. Written informed consent was obtained from all participants or their legal guardians.

2.2. Interventions and Management

Sixty minutes before the surgery, after securing 18G venous catheter, all patients received 20 mg Famotidine IV. Ringer solution was infused for intravascular volume loading before SA.

The vital signs were monitored, including electrocardiography, non-invasive blood pressure measurement and pulse oximetry (SpO₂). Spinal injection was performed under aseptic technique in the sitting position at L3-L4 or L4-L5 intervertebral space using a 27-G Quincke needle. Group F received 2.5 ml of hyperbaric bupivacaine 0.5 % plus 25 µg fentanyl, and Group C received 2.5 ml of hyperbaric bupivacaine 0.5 %.⁶ The patients were laid down supine and oxygen initiated at a rate of 6 L/min via a facemask throughout the procedure.

The level of sensory block was confirmed with sensation to cold. The accepted level for surgery was at T4-T5 level. The motor block was monitored using Modified Bromage scale. The blood pressure and heart rate were recorded at regular intervals.

The incidence of intraoperative STP was noted. To exclude abdominal or visceral origin of pain, a leading question was asked to patients to indicate the site of that pain after any complain. The severity of that pain was assessed using the numerical rating scale (0-10) at the time of complaint. Based on the score, the pain was categorized as mild (0-3), moderate (4-7) and severe (8-10). The STP was monitored every 2 h for 8 h postoperatively. If the pain was more than mild, rescue

Table 1: Demographic data and the proposed contributing factors in STP

Parameter		Group C (n = 22)	Group F (n = 22)	P-value
Age (y)		31 ± 4.9	29 ± 4	0.4 [†]
ASA	II	22 (100)	19 (86.4)	0.116 [‡]
	III	-	3 (13.6)	
No. of C. sections	Primigravida	5 (22.7)	6 (27.3)	0.5 [†]
	Multipara	17 (77.3)	16 (72.7)	
Patients' positions	Flat	20 (90.1)	19 (86.4)	0.375 [‡]
	Anti- Trendelenburg	2 (9.9)	3 (13.6)	
Irrigating fluid used		1 (4.5)	5 (22.7)	0.08 [†]
Average blood loss (ml)		684 ± 284	832 ± 113	0.03 ^{*†}
<i>Values are presented as mean ± SD or number (%). * Indicates significance, † indicates Student's t-test, ‡ indicates Fisher exact test</i>				

analgesia was given in a step ladder approach to start with ketorolac 30 mg. Inj paracetamol 1 gm, followed by pethidine 25-50 mg were added according to the response.

The number of previous CS, the irrigating fluid used, intraoperative position, and the blood loss were recorded.

2.3. Statistical analysis

Data were analyzed using Microsoft Excel 365. Numerical data are presented as mean and SD. Categorical data are presented as counts and percentages and the differences are compared using the chi-squared test or Fisher's exact test. P < 0.05 is considered statistically significant.

3. RESULTS

A total of 44 parturient undergoing elective LSCS under SA were enrolled in our study, and there was no statistically significant difference between both groups in terms of demographic data and the proposed contributing factors in STP except for intraoperative average blood loss which was higher in the fentanyl group (Table 1).

As regard intraoperative hemodynamics the mean arterial systolic pressure was statistically equivalent between both groups, whereas there was a significant difference as regards the mean diastolic pressure and heart rate (Table 2), (Figure 2).

Three patients experienced STP in the Group F while 4 patients in the Group C, which is statistically insignificant. In the fentanyl group the pain didn't last for more than 4 h during observation but in the control

group one patient had pain for as long as the observation time of 8 h (Table 3).

The pain severity was higher in Group C vs Group F where 3 patients suffered moderate pain vs one patients in Group F, but the difference wasn't statistically significant (Table 4).

The need for the opioid narcotics to control the pain was higher in Group C than in Group F, but the difference in analgesic needed between the groups was not significant (Table 5).

Point biserial correlation revealed a positive correlation (0.3) between the STP and total blood loss for the cases, however this correlation was statistically not significant ($P = 0.06$) (Figure 3).

Table 2: Mean systolic, diastolic blood pressures and heart rate in the two groups.

Parameter	Group C (n = 22)	Group F (n = 22)	P value
Systolic blood pressure (mmHg)	123 ± 11	119 ± 10	0.078†
Diastolic blood pressure (mmHg)	74 ± 6.5	72 ± 8.5	0.018*†
Heart rate (beats/min)	84 ± 6	79 ± 12	0.014*†

*Values are presented as mean ± SD. * indicates significance, † indicates Student t test.*

Table 3: Comparative number of patients suffering from shoulder tip pain at different times of surgery

Shoulder tip pain	Group C (n = 22)	Group F (n = 22)	P value
Intraoperative	4 (18.2)	3 (13.6)	0.293‡
At 2 h	4 (18.2)	3 (13.6)	0.293‡
At 4 h	4 (18.2)	2 (9.1)	0.239‡
At 6 h	2 (9.1)	0 (0.0)	0.244‡
At 8 h	1 (4.5)	0 (0.0)	0.5‡

Values presented as number (%). STP: shoulder tip pain. ‡ indicates Fisher exact test.

4. DISCUSSION

Shoulder tip pain is a distressing complaint of parturients especially while caring for their babies. The incidence varies from 6% to 68% in different studies. In our study the incidence was 16%.

A referred pain brought on by the phrenic nerve has been proposed as the cause of this pain. The iliopsoas and diaphragm muscles are both innervated by the phrenic nerve, which is derived from C3-C5 nerve roots. Additionally, it carries sensory fibers from the inferior surface layers of the parietal peritoneum. As a result, any tension on the diaphragm or parietal peritoneum can trigger the phrenic nerve. The C5 nerve is stimulated as a result, sending pain signals to the dermatomes of the musculocutaneous, radial, median, and axillary nerves.⁹

STP is significantly aided by the release of acute-phase proteins, such as hs-CRP. Hence, a higher level of high sensitivity-CRP is linked to a greater intensity of STP.¹⁰

The literature about the effect of type of anesthesia on STP shows contradicting results. In the study by

Cift et al., the incidence of STP was higher in parturient receiving general anesthesia compared to those receiving SA. Phelps study also suggested that SA is correlated with a significant reduction in the frequency and severity of shoulder pain.^{1,11} Whereas the study by Şimşek et al.

showed that STP was on the other hand more in

Table 4: the severity of pain among the patient's population who suffer a shoulder tip pain

STP severity	Group C (n = 22)	Group F (n = 22)	P Value
No	18 (81.8)	19 (86.4)	0.293
Mild	1 (4.5)	2 (9.1)	
Moderate	3 (13.6)	1 (4.5)	
Severe	0 (0.0)	0 (0.0)	

Values are presented as number (%). STP: shoulder tip pain

Table 5: Additional analgesics required among the two groups

Additional analgesics	Group C (n = 22)	Group F (n = 22)	P value
No analgesics	18 (81.8)	19 (86.4)	0.293‡
NSAIDs/ Paracetamol	0 (0.0)	0 (0.0)	
NSAIDs + Paracetamol	0 (0.0)	1 (4.5)	
Narcotics	4 (18.2)	2 (9.1)	

Values are presented as number (%). ‡ Indicates Fisher exact test

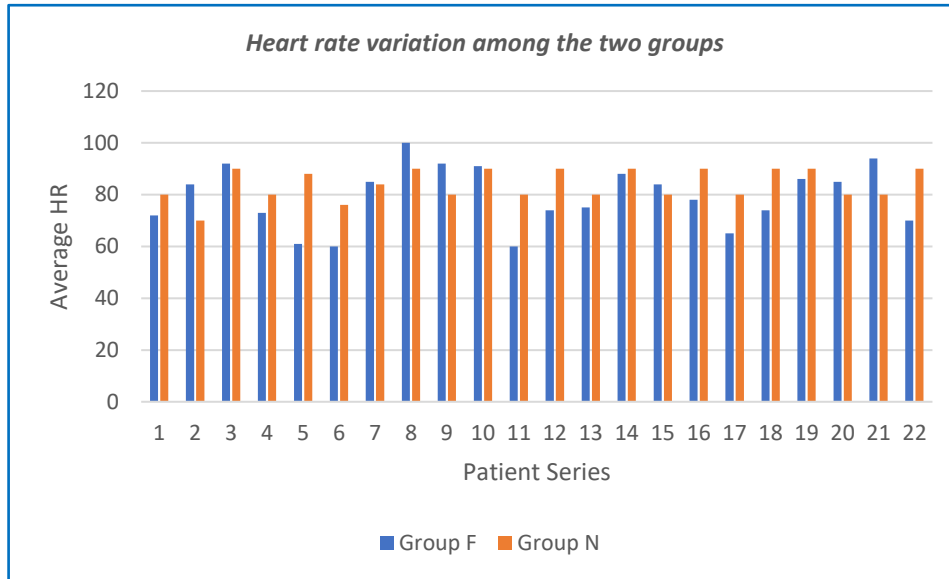


Figure 2: Comparative heart rate variation among the two groups

parturients receiving SA. Another finding from the Zirak study is that patients under SA experience more postoperative shoulder pain than those under general anesthetic; this difference may be related to how the patients are positioned before, during, and after surgery.^{6,12}

Different modalities including both pharmacological and non-pharmacological options have been explored to reduce the incidence and severity of STP. Maryam and colleagues studied the effectiveness of auriculotherapy and recommended for the use of auriculotherapy for the prevention and alleviation of shoulder pain after a CS.¹³

Placing towels around the uterus before delivering the neonate is a new technique used by Mohamed et al. and

has shown efficacy in reducing the incidence of STP as well as opioid consumption.¹⁴

Prophylactic use of ketorolac has shown to be of value in reducing the occurrence of STP as shown in the studies by Abbas and colleagues and Dehghanpisheh et al. which also have favored the use of paracetamol as another alternative to alleviate STP.^{3,5}

Another pharmacological measure studied is ketamine and dexamethasone given after SA and have been used successfully to relieve shoulder pain after CS.⁴

Intrathecal fentanyl and dexamethasone as additives to bupivacaine reduced the severity and incidence of shoulder pain in patients undergoing laparoscopic ovarian cystectomy when compared to bupivacaine alone as demonstrated by Hamed and colleagues. Consistent with these results. Sung et al. showed that the addition of 10 µg fentanyl to bupivacaine was found to reduce the incidence of shoulder tip pain by 25% during laparoscopic inguinal hernia repair under SA.¹⁵

However, our study didn't show statistically significant value from adding fentanyl to bupivacaine on STP during CS on the incidence and severity of shoulder tip pain. Our study showed a positive correlation between

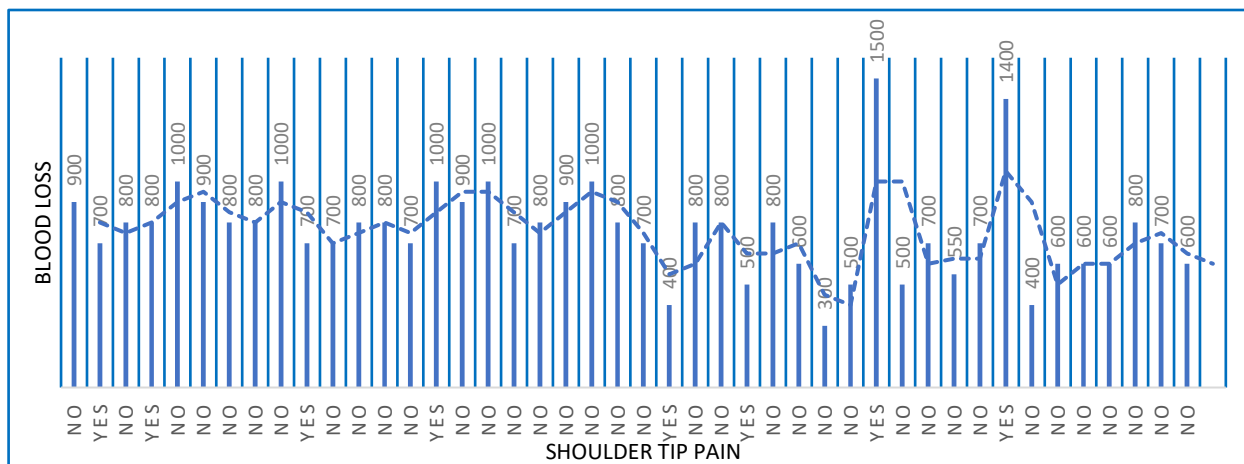


Figure 3: Point biserial correlation revealed a positive correlation (0.3) between the shoulder tip pain and total blood loss for the cases, however this correlation wasn't statistically significant P = 0.06

the STP and total blood loss for the cases; although this correlation wasn't statistically significant. This goes in line with Zirak study who measured the duration of surgery and the amount of bleeding as pathophysiological factors of shoulder pain.¹¹

5. CONCLUSION

In conclusion, this study suggests that activation of G protein linked receptor decreases the incidence of shoulder tip pain among the studied group; however, it was statistically insignificant. It gives a better hemodynamic response and decrease the need for opioid narcotics to control shoulder pain.

7. Data availability

The numerical data generated during this research is available with the authors, and can be provided on request.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

AMH: Literature search, Conception & design, Manuscript preparation, Manuscript editing, Manuscript review.

WYK: Reviewing articles, Study idea and design, Writing results section, Data collection, Data analysis, Manuscript editing, Manuscript review.

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