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Research Article

Analgesic efficacy and safety of absorbable gelatin sponge soaked with bupivacaine or bupivacaine and lidocaine in Cesarean section wounds.

Omyma S. Mohamed[1], Neven M. Nour El-Din[2], Hazem A. Abd El-Zaher[1] and Nagy S. Ali[1]

[1]Department of Anesthesia and Intensive Care, Faculty of Medicine, Minia University, Egypt
[2]Department of Gynecology and Obstetrics, Faculty of Medicine, Minia University, Egypt

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Abstract

Background: Management of acute postoperative pain is one of the major challenges after CS. Administration of local anesthetic through wound instillation is an alternative to avoid opioids drawbacks. The aim of the study is to evaluate and compare the efficacy and safety of placement of subcutaneous gelatin sponge soaked with either bupivacaine 0.25% or a mixture of bupivacaine 0.25% and lidocaine 2% for postoperative analgesia after elective CS under general anesthesia. **Methods:** A total 105 parturient were equally allocated into either: *Group C (control*): received gel-foam soaked with 20 ml of 0.9% normal saline, *Group B*: received gel-foam soaked with 20 ml bupivacaine 0.25% or *Group BL*: received gel-foam soaked with a mixture of 10ml bupivacaine 0.25% and 10 ml lidocaine2%. Perioperative heamodynamics, visual analogue scale for pain (VASP), 1st analgesic request, total analgesic requirements, side effects and wound healing were recorded. **Results:** significantly lower heamodynamics, VASP at 1, 2, 8, 12& 24 hrs. and postoperative nausea and vomiting with lower total analgesics consumption were recorded in B&BL groups compared to C group. Analgesia was of earlier onset in BL group but more intense at 4hrs. in B group, otherwise the two groups were comparable. No wound healing complications were recorded in all groups. **Conclusion:** Gelatin-sponge soaked with bupivacaine or a mixture of lidocaine and bupivacaine in CS wounds was safe and effective in providing better heamodynamics and postoperative analgesia which was earlier in onset in mixture group but more profound in bupivacaine group with narrow clinical difference between the two groups.

Keywords: bupivacaine, lidocaine, gelatin sponges, postoperative analgesia.

Introduction

Childbirth is a vital enjoyment in a woman's life, taken the many millions of births each year. A rising CS rates worldwide is observed which has implications on postoperative maternal health status. The occurrence of postpartum pain that interferes with the day-by-day activities in even a small percentage of women will have a big socioeconomic impact [(1,2)]. Disruption in the woman's mobilization and care of her baby, lower rates of breastfeeding and postpartum depression due to postoperative pain is another negative aspect of cesarean delivery [(3)]

Opioids are commonly used for relief of postoperative pain after caesarean section, either by using intrathecal administration prior to section or postoperative parenteral administration [(4)] but, opioid usage is associated with many unwanted side effects such as nausea, drowsiness, and vomiting [(5)].

Thus, there are needs for alternative analgesics to reduce the consumption of opioids. Because surgical pain originates from the surgical wound, a rational technique to perioperative pain treatment has been directed towards the use of local anesthetic infiltration on the site of

surgery, as this technique is effective, with minimal side effects, inexpensive- and without need for expertise [6].

Local anesthetics (LA) can be injected via catheters placed in surgical wounds to offer post-operative analgesia by both single shot and continuous infiltration, however, conflicting reports and different views are encountered towards this issue [7].

Absorbable gelatin sponge (gelfoam) is a porcine-derived, PH neutral, not water- soluble hemostatic material for local application that can be used during surgery in situations where conventional homeostasis is problematic. It adheres to bleeding sites and because of its uniform porosity, can absorb multiples of their weight in fluid. When inserted in the tissues, it could take a period of 2-4 weeks until complete dissolution (8,9) In addition to its hemostatic effect, gelfoam can be employed as a drug reservoir and could provide continuous release of these absorbed retained agents (10,11) Thus, this study tried to investigate the hypothesis of analgesic efficacy of subcutaneously placed gelfoam soaked with bupivacaine or a mixture of bupivacaine in halving dose and lidocaine after caesarean section and its impact on hemodynamics. With **primary endpoint:** the time of first analgesic request and **secondary endpoints:** The changes in hemodynamics, VASP, the total post-operative analgesic consumption. incidence of any side effects and wound healing.

Methodology:

After institutional approval and informed consents obtained from all patients, this prospective, double-blind, randomized, placebo-controlled study was carried out at the department of anesthesia and intensive care in Minia University Hospital of gynecology and obstetrics during the period from October 2015 till January 2017 on a total 105 women, aged 18-35y, (ASA) physical status II who under-went elective caesarean section under general anesthesia due to medical conditions (e.g. coagulopathy) or refusal of the patient to regional anesthesia. Parturient with allergy to any of the used medications, previous pelvic surgery or chronic pelvic pain, opioid addiction, psychiatric disorders, inability to understand VAS or previous complicated caesarean section were excluded.

On enrollment into the study, the participants were randomly allocated (fig.1) into three groups of 35 patients each using computer generated table and randomization sequence was concealed in sealed envelopes assignment held by an assistant who also prepared the studied medications but not involved in the clinical management or data collection. The protocol was opened after the study had been completed. Control group (C group) received gel-foam soaked with 20 ml of 0.9% normal saline, bupivacaine group (B group) the gel-foam soaked with 20 ml bupivacaine 0.25% and bupivacaine – lidocaine group (BL group) treated with gel-foam soaked with a mixture of 10ml bupivacaine 0.25% and 10 ml lidocaine2%.

Anesthetic management:

All patients received preoperative evaluation and physical examination and were instructed on how to use a 10cm VAS diagram for measurement of their postoperative pain. On arrival to the operative room, arterial blood pressure, ECG, and pulse oximetry monitors (Mindray monitor, model: IMEC12- China) were applied. The basal hemodynamics were recorded then, intraoperatively at 5, 15, 35, 45 min. and postoperatively at 10, 30 mins, 1, 2, 4, 8, 12, 18 and 24 h.

An intravenous 20 G cannula was inserted, and the patients received 5 ml/kg of 0.9% saline and were pre-oxygenated with 100% oxygen via a well fitted mask for 3 minutes or 4- 5 vital capacity breaths.

The patient was positioned in a supine position with a left lateral tilt. Induction of anesthesia was carried out after the patient was catheterized, abdominal skin decontaminated, draped and the surgical team was scrubbed.

A standardized anesthesia protocol was performed by thiopental for induction at 5 mg/kg, succinyl-choline at 1.5 mg/kg for tracheal intubation with cricoid pressure was applied until endotracheal intubation was confirmed and the cuff of the tube was inflated. Anesthesia was then maintained with isoflurane in oxygen and non-depolarizing muscle relaxant recuronium of 0.6 mg/kg after the return of spontaneous breathing with mechanical ventilation started. Surgery was performed in all cases with Pfannenstiel incision. After delivery of the baby and umbilical cord

clamping, 20 IU of oxytocin diluted in 1000 ml of 0.9% saline, fentanyl 1µg.kg and prophylactic antibiotics were administered intravenously with reversal of the left lateral tilt position of the surgical table. Near the end of surgery, absorbable gelatin sponge (gel-foam) (Curamedical B.V.

The Netherlands, Amesterdam) (Fig.2) was prepared by an assistance under complete aseptic condition, removing the sterile compressed sponge from its packaging, cutting it into desired sizes convenient to the wound size then immersed in sterile saline and then withdrawn, squeezed between gloved fingers to expel air bubbles. Also the studied medications, either 0.9% normal saline (Otsuka Ateco Pharma, Egypt), bupivacaine 0.25% (MYLAN S.A.S., France) or lidocaine2% (Grand Pharma, Egypt) were prepared in similar sterile coded syringes and supplied to the surgeon before skin closure in a double blinded fashion (neither the patient nor the investigator, the surgeon, or any of the medical care givers were aware of the group assignment) to place the gel-foam in the wound subcutaneously and inject the prepared medications into it, then close the incision.

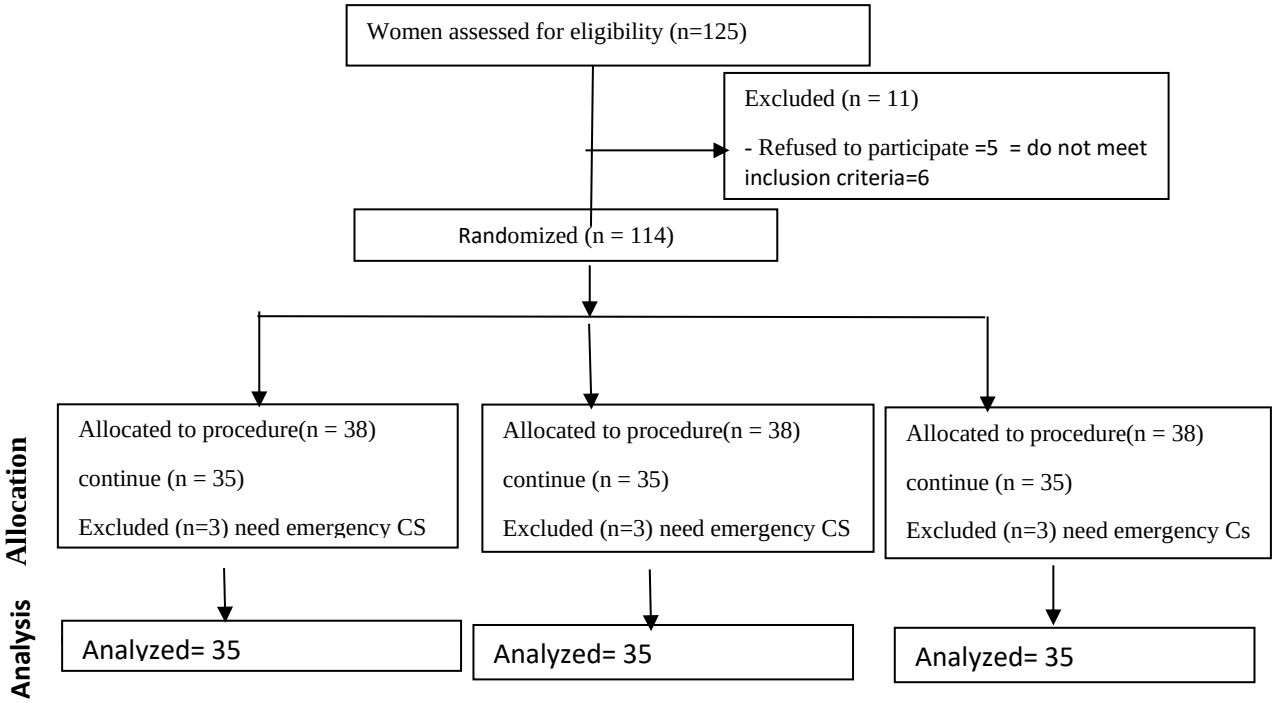

Figure (1): Flow chart

Figure (2): Absorbable Gelatin sponge before unpackaging

Reversal of residual neuromuscular blockade was done by using appropriate doses of neostigmine and atropine during the skin closure and after spontaneous respiration returned. Postoperatively, all patients received routine postoperative care and postoperative pain was assessed at 1, 2, 4, 8, 12, 18 and 24 hrs by visual analogue pain scale score (VAPS) which consists of a straight line with the endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be, if it was ≥4, ketorolac 30mg IV was given at 6 hours intervals at least with a maximum dose of 120mg/day, if the analgesia was not adequate intravenous fentanyl at 1mic/kg was given. The time of 1st analgesic request (time elapsed from the end of surgery until the first patient's request for analgesia or if VAPS >4), number of patients needed analgesia and total analgesic requirement over 1st 24hrs was calculated. Also, the patients were followed up for any side effects e.g., allergic reactions, toxicity, pruritus, nausea and vomiting and also for wound healing.

Statistical analysis

The collected data were analyzed using SPSS program software version 20. For Parametric quantitative data, descriptive statistics were done by mean, SD and min& max. of the range, and for non-parametric quantitative data by median and IQ range, while done for categorical data by number and percentage. One Way ANOVA test was used for parametric quantitative data between the 3studied groups followed by Post Hoc Tukey correction between each 2 groups, and for non-parametric quantitative data between the 3 groups using Kruskal Wallis test followed by Mann Whitney test between each 2 groups. Within individual group, paired sample t test used for parametric quantitative data and Wilcoxon signed rank test. for qualitative data. The level of significance was taken at (P value < 0.05).

Sample size calculation: The required number of patients in each group was determined after a power calculation according to data obtained from a pilot study which reported the mean time of 1st analgesia in each group and 105 patients was determined to provide 80% power for one way ANOVA test at the level of 5% significance using G Power 3.1 9.2 software.

Results

As shown in (Table 1), the three groups were comparable as regard age, weight, and operative time. Hemodynamics were comparable preoperatively and intraoperatively in all studied groups. Postoperatively, B & BL groups recorded significantly lower HR at all-time points and lower MAP up to 2 hrs. compared to C group with no significant difference was detected between each other (Fig 3 and Table 2). Regarding postoperative VASP, it was significantly lower in group B and BL in comparison to group C at all time-points, The only detected difference between B and BL groups was significantly lower VAPS at 1hr in BL group but it reversed to be in B group at 4 hrs. (i.e. earlier onset of analgesia in BL group but more intense in B group (table 3) consequently, significantly longer time to 1st analgesic request was detected in group B (4.81±3.65, *P-value* 0.001) and group BL (4.33±1.94, *P-value* 0.001) when compared to the control group (1±0) with significantly lower number of patients who needed analgesia & total amount of postoperative 24h analgesics requirement (Fig. 4, Table 4). Significant higher incidence of postoperative nausea and vomiting was detected in the control group with more consumption of anti-emetics in comparison to B and BL groups with insignificant difference between the therapeutic groups. No complications regarding wound healing or the surgical site were recorded in all groups (Table 4)

Table (1): Demographic data

Variable	Group C (n=35)	Group B (n=35)	Group BL (n=35)	P value
Age (years) Mean ± SD	26.51±4.05	26.8±4.83	27.22±4.83	0.807
Weight (Kg) Mean ± SD	91.77±5.93	88.45±15.26	87.57±13.79	0.329
Operative time(mins) Mean ± SD	42.4±1.39	43.65±4.26	43.05±4.53	0.368

- data presented as mean +SD or %

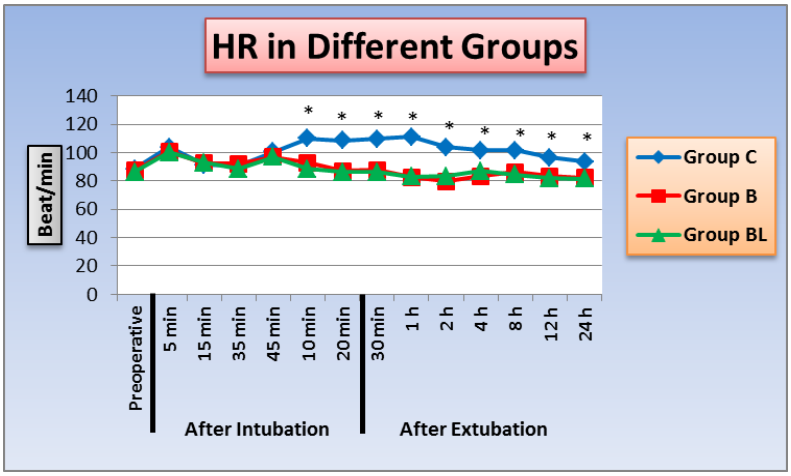

Figure (3): The changes in the mean heart rate (HR) in the studied groups (beat/min)

Table (2): Changes in the mean arterial blood pressure (MAP) (mmHg)

Time	Group C (n=35)	Group B (n=35)	Group BL (n=35)	P value
Preoperative Mean ± SD	91.28±5.66	92.52±11.25	93.85±10.09	0.516
After intubation				
5 min Mean ± SD	# 102.09±7.18	# 106.04±10.89	# 106.38±13.53	0.190
15 min Mean ± SD	89.73±9.7	92.42±14.42	93.38±12.66	0.447
35 min Range Mean ± SD	88.66±7.01	(88.95±15.11	# 87.33±9.99	0.813
45 min Mean ± SD	# 101.71±5.96	97.76±16.59	96.28±16.36	0.244
After extubation				
10 min Mean ± SD	# 99.9±6.83	89.09±12.7▲	# 86.9±13.01¥	< 0.001*
30 min Mean ± SD	# 101.9±5.54	89.71±11.46▲	# 85.85±11.38¥	< 0.001*
1h Mean ± SD	# 99.33±7.78	# 88.19±11.11▲	# 85.42±9.43¥	< 0.001*
2h Mean ± SD	# 95.38±8.79	# 85.42±9.378▲	# 84.81±9.13¥	< 0.001*
4h Mean ± SD	91.95±6.74	# 88.28±10.317	90.81±13.34	0.330
8h Mean ± SD	94.28±9.02	90.7±12.525	# 90.23±9.47	0.213
12h Mean ± SD	89.33±7.25	89.71±9.847	# (87.85±8.41	0.633
24h Mean ± SD	# 85.71±6.88	# 88.04±9.697	# 86.81±8.13	0.504

- data presented as Mean ± SD) *significant difference among the groups (p<0.05)
#significant difference within the individual group (p<0.05)
▲ significant difference between C&B groups ¥ significant difference between C&BL groups

Table (3): Postoperative Visual Analogue Scale for Pain (VASP)

Time	Group C (n=35)	Group B (n=35)	Group BL (n=35)	P value
1h Median ±IQR	6 (6-7)	3 (3-3) ±▲	3 (2-3) ¥	<0.001*
2h Median ±IQR	# 4 (4-5)	# 2 (2-3) ▲	# 2 (2-3) ¥	<0.001*
4h Median +IQR	# 5 (4-5)	3 (3-3) ▲ ±	# 4 (3-5)	<0.001*
8h Median +IQR	# 5 (5-7)	4 (4-5) ▲	5 (4-5) ¥	0.005*
12h Median +IQR	# 4 (4-5)	# 4 (3-4) ▲	# 4 (3-4) ¥	<0.001*
18h Median +IQR	# 3 (3-4)	3 (3-3) ▲	3 (2-3) ¥	<0.001*
24h Median +IQR	# 3 (3-3)	2 (2-2) ▲	# 2 (2-2) ¥	<0.001*

Data presented as median ± IQ range *significant difference among the groups (p<0.05)
#significant difference within the individual group (p<0.05)
▲ significant difference between C&B groups
¥ significant difference between C&BL groups ± significant difference between B&BL groups

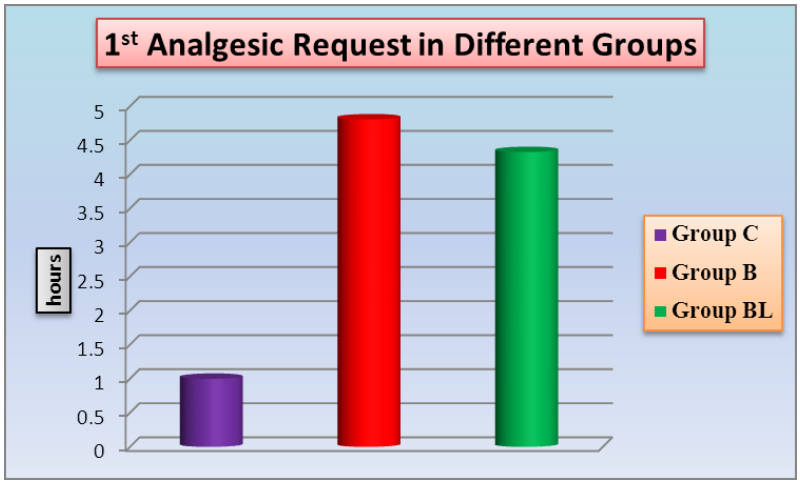

Figure (4): Time to 1st analgesic request (hrs.) among the groups

Table (4): Number of patients required analgesia, total analgesic &antiemetic consumption

Variable	Group C	Group B	Group BL	P value
Analgesic request No Yes	 0(0%) 35(100%)	 24(67.6%) 11(32.4%)▲	 17(48.6%) 18(51.4%)¥	 <0.001*
Total amount of fentanyl (µg/person) Mean ± SD	90±10	49.44±15.32▲	62.72±23.59¥	<0.001*
Total amount of ketorolac (mg/person) Mean ± SD	96±12.17	63.33±10.02▲	78±16.43¥	<0.001*
Antiemetic request Yes No	 74.3% 25.7%	 88.6% 11.4%	 91.4% 8.6%	 <0.001*

data presented as no., percentage or mean + SD *significant difference among the groups (p<0.05)
▲ significant difference between C&B group ¥ significant difference between C&BL groups

Discussion

The proof of the benefits of a single dose of local anesthetic in the cesarean wound is restricted and contradictory. In 2010, it was noticed that bupivacaine infiltration in the surgical site decreased the amount of rescue morphine consumption after Cesarean section in women operated under general anesthesia [12]. Bupivacaine-soaked sponges appear relatively cost-effective, easy to perform, and feasible even in less-resourced regions, from this concept, and due to the raising number of patients requiring general anesthesia either by their well or those who are contraindicated to regional anesthesia, this study, attempted to evaluate and compare the analgesic effect of gelatin sponges soaked with either bupivacaine or a mixture of bupivacaine with lidocaine (to combine the rapid onset of lidocaine and long duration of bupivacaine) when placed subcutaneously in cesarean section wound as an attempt for reduction of opioid consumption with a concomitant decrease in opioid-related side effects.

Our results detected that the studied technique produced more hemodynamic stability, rapid onset of analgesia, delayed time of first analgesic request, decreasing the total amount of postoperative analgesics with less incidence of nausea and vomiting in comparison to the control group. The two therapeutic groups were nearly comparable at all time intervals apart from that bupivacaine group was superior to some extent in achieving more intense analgesia at the time of 4 hrs. postoperatively (due to larger volume of bupivacaine was received) with statistically insignificant longer time of first analgesic request(4.81±3.65vs 4.33±1.94) than the mixture group, however the later showed a significant rapid onset of analgesia as lidocaine hasten the onset of action in BL group, otherwise the clinical difference was narrow between the two therapeutic groups. The reservoir action of the gelatin sponges for local anesthetics to be released sustainably, provided a higher drug concentration in the cesarean section wound and played a vital role in prolonging the drug effect which permits the woman to feel more relaxed and comfortable.

The favorable actions of the LA soaked gelfoam detected in present study agree with those of other investigators who found that pain scores and the total analgesic requirement were lower in parturient treated with suprafacial bupivacaine-soaked gelatin sponges in comparison to those in the control group during the first postoperative eight hours [9].

Similarly, other clinical trials recorded lower pain score with lower postpartum total analgesic in women received bupivacaine-soaked spongostan placed in episiotomy bed [11,13] than those treated with local lignocaine infiltration and the difference was statistically significant at all-time intervals during the first 24 hours [13].

On contrary, local application of bupivacaine soaked gelfoam at the site of iliac graft operations failed to reveal any significant difference in VAS pain scores in comparison to the use of parenteral opioid although the required narcotic dosage was significantly less in bupivacaine group at 24 and 48 hours [14].

Compared with lidocaine, bupivacaine possess a longer duration of action but slower onset which make it not a perfect sole LA in some situations, thus, combining them together can provide the best of both. Also, lidocaine has a competitive effect with bupivacaine at the binding sites of sodium channels with a strong suggestion of lidocaine ability to counteract the cardiac toxicity the most dangerous side effect of bupivacaine [15]. This point was one of the main goals of this research as lowering the volume or concentration of the used LA and obtaining the same or nearly equal effect is a target in itself. In a comparative study, different concentrations of intradermal lidocaine (0.5% and 1%) and bupivacaine (0.125% and 0.25%) and combinations of them in addition to epinephrine were investigated where the results showed narrow clinical benefit presented by longer duration of the action in combination groups while the onset was not statistically different [16]

Side effects and complications are vital and must be recorded and analyzed whenever a new procedure is implemented in clinical practice. In the current research, significantly lower incidence of nausea and vomiting was found in bupivacaine and bupivacaine-lidocaine groups compared to the control group, and no complications were recorded related to the surgical wound in all groups.

On the same context, other studies found the frequency of postoperative nausea, vomiting and antiemetic requirement were lower in the group treated with bupivacaine soaked gelfoam with similarly low rates of wound erythema and infection as that of the control group [9]. Also, excellent safe hemostatic effect without any recorded complications was obtained when gelatin sponge was used as hemostat in wounds of thyroid surgery [17]

The current study has a number of limitations that the peak plasma concentration, plasma half-life, and total clearance of the used dosages of the studied agents were not investigated. Also, there was some shortage in the data concerning the long term follow up and if any complaint of chronic pain occurred after caesarean section as the duration of hospitalization was short.

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