

July 30, 2020

Ehab Farag  
Academic Editor  
PLOS ONE

Dear Dr. Farag

Please find attached the revised version of our manuscript PONE-D-20-14430 entitled “The incidence of chronic pain following Cesarean section and associated risk factors: a cohort of women followed up for three months”. We thank the reviewers for their invaluable contributions, all of which have been taken into consideration in this revision and which have certainly improved and given greater consistency to the text. Our point-by-point answers to the reviewers’ questions are detailed as follows:

#### **Reviewer 1**

**Comment:** Line 81 please add "elective" before Cesarean

The reviewer’s suggestion implies that the description of the study population was not clear; therefore, we decided that the text should be improved. The present study sample described in the manuscript was indeed made up of women who had been submitted to an elective Cesarean section, i.e. prior to the onset of labor and rupture of the membranes [1,2]. Nevertheless, the main study in which this study was nested included all the women admitted for a Cesarean section (n=1,122) irrespective of whether or not the procedure was elective. For this reason, we decided not to include the term “elective” before “Cesarean section” in that specific segment, as suggested by the reviewer, since this would lead to the interpretation that only women submitted to an elective Cesarean section had participated in the larger main study, which was not the case. Therefore, to improve our description of the study population, we have rewritten the relevant segment of the Methods section (page 4, lines 80-85), as follows:

*“For the larger main study, 1,122 women who were admitted to hospital for a Cesarean section were recruited. The present study included only those who underwent an elective Cesarean section and who did not meet the following exclusion criteria: age <20 years, presence of pain in the pelvic region that preceded pregnancy, women who had requested that tubal ligation be*

*performed during the Cesarean section, women who had difficulty in communicating verbally, and those in continuous use of opioids.”*

**Comment:** Is there a role of prior C Section on chronic pain? Please elaborate on the incidence of chronic pain in primary versus repeat C section

There is some evidence that previous surgeries may play a role in the chronification of postoperative pain [3–6]. This may occur due to repeated exposure to postoperative pain treated with opioids, resulting in central sensitization and hyperalgesia [5] and/or to the increased risk of nerve entrapment caused by the increase in fibroses at repeat surgeries [6]. Consequently, we analyzed the effect of exposure to a prior Cesarean section and the occurrence of chronic postoperative pain. These results are shown in Table 2 (page 12). In agreement with other studies with similar populations [7–13], there was no statistically significant difference between the incidence of chronic postoperative pain in women who had been submitted to a previous C-section and those who were undergoing the procedure for the first time.

## **Reviewer 2**

**Comment:** What analgesics did patients receive in postoperative period other than dipyrone?

Thank you for this question. Data regarding the medication received for pain relief were collected postoperatively for all the women in the cohort (n=620) while they were still in hospital. We have now added further information on this subject in the Results section (page 10, lines 179-184), as follows, and have added an extra table (S1 Table) in the Supporting Information section.

*“Of the 620 women monitored after surgery, all received some type of medication for pain relief while in hospital. As shown in S1 Table, almost all (99.7%) were given simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) (93.3%) during this period. Of the simple analgesics, dipyrone was the most commonly administered medication (99.2%), while, of the NSAIDs, diclofenac sodium was the most common (99.5%). Only five women (0.8%) were given an opioid analgesic during this period”.*

## Supporting information

S1 Table. Medication received postoperatively during hospitalization.

Medication received as pain relief <sup>a</sup>	Women (n=620)	
	n	%
<b>Simple Analgesics<sup>b</sup></b>	612	99.7
Dipyrone	607	99.2
Acetaminophen	5	0.8
<b>NSAIDs<sup>c</sup></b>	571	93.3
Diclofenac sodium	568	99.5
Tenoxicam	111	19.4
<b>Opioids<sup>b</sup></b>	5	0.8
Tramadol	5	100.0
<b>Combination drugs<sup>b</sup></b>	5	0.8
Caffeine + carisoprodol + diclofenac sodium + acetaminophen	4	80.0
Codeine phosphate + acetaminophen	1	20.0

<sup>a</sup>The women may have taken more than one type of pain relief medication; <sup>b</sup>Data missing=6; <sup>c</sup>Data missing=8; NSAIDs: Non-steroidal anti-inflammatory drugs.

### **Comment:** Do you allow partner's presence during cesarean section to reduce anxiety?

Not all of the women were able to have an accompanying person in the operating room, since permission for a companion to be present in the hospital where data collection was performed was dependent on authorization from the attending surgeon. In this study, data are not available on this factor since this information was not collected in a standardized manner.

### **Comment:** Do patients receive analgesic when they were in pain after 7 days of surgery?

### **Comment:** Did patients demand analgesic at 60 and 90 days?

Yes, some of the women were in use of pain relief medication during follow-up. The reviewer's question made us reconsider how this information was provided in the manuscript and we decided to add a paragraph in the Results section and include some supplementary tables (S2-S5 Tables) regarding the use of pain medication during follow-up.

Since information was included on the use of medication at all evaluation moments during follow-up, we deemed it relevant to also present related data in the flowchart of the cohort. Therefore, we have changed the flowchart to add the number of women evaluated at 30 and 60 days following surgery (Fig 1).

The following paragraph was included in the manuscript (page 10, lines 185-192) and refers to the additional tables:

*“Following discharge from hospital, 95.8%, 36.0%, 15.5% and 17.0% of the women with surgery-related pain used some form of pain relief medication on the 7<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup> and 90<sup>th</sup> day after the Cesarean section, respectively. Of the women who used simple analgesics, dipyrrone was the drug of choice at all the evaluation moments (7<sup>th</sup> day = 95.9%; 30<sup>th</sup> day = 87.2%; 60<sup>th</sup> day = 91.7% and 90<sup>th</sup> day = 90.9%). Of those who used an NSAID, diclofenac sodium was the most commonly used drug throughout follow-up (7<sup>th</sup> day = 97.9%; 30<sup>th</sup> day = 92.3%; 60<sup>th</sup> day = 90.0% and 90<sup>th</sup> day = 71.4%). None of the participants used an opioid following discharge from hospital (S2-S5 Tables)”.*

## Supporting information

S2 Table. Use of medication by the women with pain on the 7<sup>th</sup> day following surgery (n=434).

Pain relief medications <sup>a</sup>	Women (n=434) <sup>b</sup>	
	n	%
<b>Use of pain relief medication</b>	409	95.8
<b>Simple Analgesics</b>	319	78.0
Dipyrrone	306	95.9
Acetaminophen	16	5.0
<b>NSAIDs</b>	335	81.7
Diclofenac sodium	328	97.9
Nimesulide	6	1.8
Naproxen	1	0.3
Ibuprofen	1	0.3
<b>Combination drugs</b>	8	2.0
Caffeine + carisoprodol + diclofenac sodium + acetaminophen	2	25.0
Dipyrrone + promethazine hydrochloride + adiphenine hydrochloride	5	62.5
Carisoprodol + diclofenac sodium + acetaminophen + caffeine	1	12.5

<sup>a</sup> The women may have taken more than one type of pain relief medication; <sup>b</sup> Data missing=7; NSAIDs: Non-steroidal anti-inflammatory drugs.

S3 Table. Use of medication by the women with pain on the 30<sup>th</sup> day following surgery (n=173).

Pain relief medications <sup>a</sup>	Women (n=173) <sup>b</sup>	
	n	%
<b>Use of pain relief medication</b>	58	36.0
<b>Simple Analgesics</b>	39	67.2
Dipyrone	34	87.2
Acetaminophen	5	12.8
<b>NSAIDs</b>	26	44.8
Diclofenac sodium	24	92.3
Ibuprofen	1	3.8
Nimesulide	1	3.8
<b>Combination drugs</b>	1	1.7
Dipyrone + orphenadrine citrate + anhydrous caffeine	1	100.0

<sup>a</sup> The women may have taken more than one type of pain relief medication; <sup>b</sup> Data missing=12; NSAIDs: Non-steroidal anti-inflammatory drugs.

S4 Table. Use of medication by the women with pain on the 60<sup>th</sup> day following surgery (n=147).

Pain relief medications <sup>a</sup>	Women (n=147) <sup>b</sup>	
	n	%
<b>Use of pain relief medication</b>	22	15.5
<b>Simple Analgesics</b>	12	54.5
Dipyrone	11	91.7
Acetaminophen	1	8.3
<b>NSAIDs</b>	10	45.5
Diclofenac sodium	9	90.0
Nimesulide	1	10.0
<b>Combination drugs</b>	1	4.5
Caffeine + carisoprodol + diclofenac sodium + acetaminophen	1	100.0

<sup>a</sup> The women may have taken more than one type of pain relief medication; <sup>b</sup> Data missing=5; NSAIDs: Non-steroidal anti-inflammatory drugs.

S5 Table. Use of medication by the women with pain on the 90<sup>th</sup> day following surgery (n=118).

Pain relief medications <sup>a</sup>	Women (n=118) <sup>b</sup>	
	n	%
<b>Use of pain relief medication</b>	19	17.0
<b>Simple Analgesics</b>	11	57.9
Dipyrone	10	90.9
Acetaminophen	1	9.1
<b>NSAIDs</b>	7	36.8
Diclofenac sodium	5	71.4
Nimesulide	1	14.3
Ibuprofen	1	14.3
<b>Combination drugs</b>	2	10.5
Caffeine + carisoprodol + diclofenac sodium + acetaminophen	1	50.0
Dipyrone + adiphenine hydrochloride + promethazine hydrochloride	1	50.0

<sup>a</sup> The women may have taken more than one type of pain relief medication; <sup>b</sup> Data missing=6; NSAIDs: Non-steroidal anti-inflammatory drugs.

**Comment:** Can you provide these severity of pain at 90 days?

Yes, the women reporting pain on the 90<sup>th</sup> day following surgery were asked about the intensity of this symptom, particularly when the pain was most intense. We have added the following segment to the Results section (page 10, lines 194-196).

*“When the women with CPSP (n=118) were asked about the intensity of pain at the moment when this symptom was most intense, 16.1%, 47.5% and 36.4% reported mild, moderate and severe pain, respectively. The mean intensity of pain was 5.7 (±2.3 SD)”.*

**Comment:** Any H/O drug abuse in the past for any of the patients?

In relation to drug abuse, prior to surgery the patients were asked about their use of opioids, alcohol and tobacco. All stated that they did not use opioids (an exclusion criterion). Data on alcohol consumption and smoking are shown in the tables. Regarding opioid use, we have now included the following phrase in the manuscript as part of the exclusion criteria in the Methods section (page 4, line 85):

*“and those in continuous use of opioids.”.*

**Comment:** Can you include the surgeon variable? (e.g. is there one or two particular surgeons whose patients had less pain or more CPSP?)

At this institute, six different surgeons perform Cesarean sections. In the present study, it was not possible to include data on the variable “*surgeon*” since this information was not collected in a standardized manner.

## REFERENCES

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