Postoperative pain inhibition by preoperative methylprednisolone in open cholecystectomy with the assessment of IL-6 and PGE₂

Suwarman and Hendro Sudjono Yuwono* 

*Correspondence: hsyabc47@gmail.com

School of Medicine, Padjadjaran University, Bandung, Indonesia.

Abstract

**Background:** Open cholecystectomy is an operation which is often carried out with the aim of removing the gallbladder. In this operation an incision was performed along a 10-15 cm line in the right subcostal or midline area under the epigastric area. Here postoperative pain is a common problem that must be taken into consideration. PGE₂ and IL-6 are the predominant cytokines that are released after trauma from surgery and associated with inflammation of pain. Methylprednisolone is a glucocorticoid that has been reported to reduce postoperative pain in addition to inhibiting hyperalgesia of inflammatory mediator IL-6 and PGE₂.

**Material and methods:** The level of pain was assessed during the 1st hour of surgery, the 2nd, 4th, 8th, 12th and 24th hour consecutively. 125 mg of methylprednisolone was injected intravenously 60 minutes before the operation and 30 minutes before completing the skin sutures. For Group I: methylprednisolone was given postoperatively; Group II: methylprednisolone was given before surgery; and for Group III, the Control Group. Each Group number included a sample of 10 patients with the following inclusion criteria: ASA clinical classification I-II, age 20-60 years.

**Results:** The study showed that the treatment reduced postoperative IL-6 levels significantly (p=0.0000), except in the 24th hour (p=0.4999). The postoperative PGE₂ was not significantly changed (p>0.05).

**Conclusion:** The levels of IL-6 in open cholecystectomy that were given methylprednisolone intravenously preoperatively were lower than given postoperatively, but were not reduced for the PGE₂ level. Methylprednisolone administered intravenously before open cholecystectomy is able to decrease postoperative pain.

**Keywords:** Methylprednisolone, open cholecystectomy, IL-6, PGE₂

Introduction

Postoperative pain occurs after open cholecystectomy. The pain is caused by stimulation of sensory nerves in injured soft tissue, particularly in the area where the skin incision occurs. The inflammatory pain occurs due to tissue damage that causes an inflammatory response caused by the release of a local mediator with systemic effect [1]. These mediators include IL-6 and PGE₂ [1,2]. The presence of inflammatory mediators contributed to the occurrence of postoperative pain. Methylprednisolone has the effect of inhibiting the formation of pro-inflammatory cytokines production by macrophages and mast cells, which then prevents cyclooxygenase from occurring [3]. Formation of cyclooxygenase leads to changes in arachidonic acid and to prostaglandins, which then prevents painful stimuli from occurring [3]. Are there differences in the levels of PGE₂ and IL-6 after open cholecystectomy surgery among patients given intravenous methylprednisolone before and after surgery?

Materials and methods

**Patients**

Patients were those undergoing open cholecystectomy surgery, ASA clinical classification I-II, age 20-60 years. We exclude patients with chronic pain, females with positive pregnancy test results, anyone taking long-term glucocorticoid, people with drug hypersensitivities to methylprednisolone, patients with diabetes mellitus, and those who would undergo cholecystectomy surgery that would last for more than 4 hours.

**Ethical clearance**

This clinical trial has been approved by the Research Ethics
Committee of the School of Medicine, Padjadjaran University. After all procedures have been explained in detail, all participant-patients should eventually signed the consent form.

**Glucocorticoid**

Methylprednisolone 125mg (Medixon, Ferron) was injected intravenously at 60 minutes before the operation and 30 minutes before completing the skin sutures.

**Open cholecystectomy**

Open cholecystectomy surgery is a gallbladder excision in patients with gallstone disorder or who have an infection in the gallbladder, which is done along a 10-15 cm line in the right subcostal area or in the midline incision.

**Anesthetic procedures**

Sixty minutes before anesthetic-induction, intravenous 125 mg methylprednisolone (Group II) was given preoperatively, while in the postoperative methylprednisolone group (Group I) and the control group (Group III), 1 cc 0.9% NaCl was given intravenously. Induction of anesthesia in both groups carried out by administering 2-3mg/kg body weight of propofol. The patients were ventilated with N2O/O2=50%:50%, and 2% volume isoflurane. General anesthesia involved an Isoflurane vaporizer and anesthesia machine (Draeger) with nitrous oxide, oxygen, isoflurane and atracurium. Intravenous fentanyl dosage 1-3 mg/kg body weight were used for analgesia during surgery.

**IL-6 and PGE2 kits**

Human IL-6 and PGE$_2$ kits, determined using ELISA, were bought from R&D system, USA.

**Statistical analysis**

This clinical trial was a double blind randomized controlled trial of patients undergoing open cholecystectomy surgery in general anesthesia.Permuted-block randomization were used.

A one-wayanova test was used when the data were normally distributed, but when the data were not normally distributed a Kruskal-Wallis test was used instead. A Shapiro-Wilk test will be used for normal distribution testing. Data analysis was performed using SPSS for Windows version 13.0 on a confidence interval level of 95% with a regarded significant value of p<0.05.

The sample size used the following formula

$$n = \frac{2(Sd)^2(Z\alpha + Z\beta)^2}{E^2}$$

$n=sample\ size; \ Sd=standard\ deviation; \ E=effect\ size; \ Z\alpha \ and \ Z\beta \ are \ the \ value \ obtained \ from \ the \ normal \ distribution \ table.$

Based on the above formula a minimum sample size $n=8$ was obtained, so the conclusion was to use a sample number of 10.

**Results**

**Patient's characteristics**

All parameters in Table 1 shows a not significance value (p>0.05). All patients with HARS<5 were participants who did not have any anxiety condition.

**Table 1. Distribution of patient's characteristic.**

| Patient's characteristic | Grouping | P-value |
|-------------------------|----------|---------|
|                         | I (n=10) | II (n=10) | III (n=10) |
| Gender:                |          |          |            |
| Man                    | 6        | 6        | 6          |
| Woman                  | 4        | 4        | 4          |
| Age (year) :           |          |          |            |
| Standard Dev.          | 42.6 (13.5) | 52.8 (11.8) | 54.2 (11.2) |
| Median                 | 45       | 53       | 53         |
| Range                  | 22-68    | 30-72    | 38-73      |
| Education :            |          |          |            |
| High school            | 4        | 3        | 2          |
| University             | 4        | 2        | 3          |
| HARS:                  |          |          |            |
| Median                 | 3.5      | 3        | 3          |
| Rentang                | 3–4(a)   | 2–4(ab)  | 2–3(b)     | 0.016$^*$

All were calculated by using the Chi-square test, except for age by t-test.

Group I: Postoperative methylprednisolone; Group II: Preoperative methylprednisolone; Group III: Control.

HARS-Hamilton Anxiety Rating Scale

**Blood level IL-6 concentration**

Table 2 shows preoperative intravenous methylprednisolone given resulted in a significant decrease of postoperative IL-6 concentration.

The results from Table 3 confirmed the results from Table 2 i.e., the significantly decreased level of IL-6 concentration in the 1st, 4th, 24th hour postoperation.

**Blood concentration level of PGE$_2$**

The results show in Tables 4 and 5 show that the postoperative concentration of PGE$_2$ was higher than the preoperative concentration of PGE$_2$.

**Discussion**

Preoperative steroid administration can lower the intensity of the postoperative pain. In suppressing postoperative pain, glucocorticoids like methylprednisolone or dexamethasone have been scientifically investigated to show that one preoperative single dose was having many advantages in reducing postoperative pain. A clinical investigation by Musba et al., (2015) showed that the 15 patients who received preoperative combination of 8 mg dexamethasone, paracetamol and morphine, had not had their IL-6 and IL-10 levels increase in immediate post-surgery and 24-hours post-operation periods [4]. The glucocorticoids have a mechanism through which...
**Table 3. Comparison IL-6 concentration between Groups.**

| IL-6 concentration (ng/mL) | Grouping | P-value |
|---------------------------|----------|---------|
|                           | I (n=10) | II (n=10) | III (n=10) |
| Preop.(Sd)                | 5.91 (8.13) | 35.47 (43.68) | 17.34 (26.98) |
| Median                    | 2.49 | 12.14 | 4.79 |
| Range                     | 0.95-28.05 | 1.61-140.0 | 0.39-68.7 |
| 1st hour postop (Sd)      | 65.30 (31.22) | 22.13 (13.68) | 61.04 (46.74) |
| Median                    | 64.05 | 18.91 | 47.07 |
| Range                     | 21.61-106.28 | 5.89-50.33 | 5.30-140.0 |
| 4th hour postop (Sd)      | 18.46 (13.24) | 13.62 (7.78) | 39.48 (21.69) |
| Median                    | 17.75 | 13.5 | 38.1 |
| Range                     | 1.10-49.82 | 3.6-24.9 | 4.36-78.07 |
| 24th hour postop (Sd)     | 24.65 (22.04) | 16.65 (15.21) | 43.53 (39.10) |
| Median                    | 16.78 | 10.66 | 29.53 |
| Range                     | 1.80-76.82 | 2.88-44.31 | 5.63-128.8 |

**Tabel 3. Comparison IL-6 concentration between Groups.**

| IL-6 concentration (ng/mL) | Grouping | P-value |
|---------------------------|----------|---------|
|                           | I (n=10) | II (n=10) | III (n=10) |
| Preop -1st hour postop    | -59.39 | 13.34 | -43.70 |
| Preop-4th hour postop     | -12.55 | 21.85 | -22.14 |
| Preop-24th hour postop    | -18.74 | 18.82 | -26.19 |
| 1st hour-4th hour postop  | 46.84 | 8.51 | 21.56 |
| 1st hour-24th hour postop | 40.65 | 5.47 | 17.52 |
| 4th hour-24th hour postop| -6.19 | -3.03 | -4.05 |

Kruskal-Wallis test.

Group I: postoperative methylprednisolone
Group II: preoperative methylprednisolone
Group III: control

Preop = preoperation; postop = postoperation.

**Table 4. PGE2 concentration.**

| PGE2, (pg/mL) in plasma | Grouping | p-value |
|-------------------------|----------|---------|
|                         | I (n=10) | II (n=10) | III (n=10) |
| Preop.(Sd)              | 711.5 (1551.8) | 2459.7 (1765.9) | 2581.0 (1506.3) |
| Median                  | 3994.8 | 2746.9 | 2593.6 |
| Range                   | 1635.2-5951.7 | 92.7-5309.2 | 259.7-5446.7 |
| 1st hour postop.(Sd)    | 2278.7 (1314.4) | 1792.9 (1015.0) | 2630.9 (1285.4) |
| Median                  | 2345.6 | 1696.6 | 2734.0 |
| Range                   | 196.8-4306.7 | 120.8-3706.8 | 819.9-4254.1 |
| 4th hour postop. (Sd)   | 3077.3 (1432.7) | 1570.4 (830.0) | 2772.0 (1220.8) |
| Median                  | 3260.6 | 1521.0 | 2303.6 |
| Range                   | 374.6-4629.3 | 362.1-2749.0 | 1635.2-4702.6 |
| 24th hour postop. (Sd)  | 2767.8 (926.4) | 1786.4 (1092.8) | 2572.4 (1552.0) |
| Median                  | 2618.6 | 1675.8 | 2739.6 |
| Range                   | 1670.8-4574.7 | 92.7-3713.5 | 92.7-5173.4 |

Kruskal-Wallis test.

Group I: postoperative methylprednisolone
Group II: preoperative methylprednisolone
Group III: control; (Sd)=(Standard deviation)
Table 5. PGE₂.

|                    | Grouping |       | p-value* |
|--------------------|----------|-------|----------|
|                    | I (n=10) | II (n=10) | III (n=10) |
| Preop - 1st hour postop | 1432.7  | 666.7 | -49.8 | 0.027 |
| Preop - 4th hour postop | 634.1  | 889.3 | -191.0 | 0.195 |
| Preop - 24th hour postop | 943.7  | 673.2 | 8.6   | 0.350 |
| 1st hour - 4th hour postop | -798.6 | 222.6 | -141.2 | 0.127 |
| 1st hour - 24th hour postop | -489.1 | 6.5   | 58.5  | 0.727 |
| 4th hour - 24th hour postop | 309.5  | -216.1 | 199.6 | 0.272 |

Kruskal-Wallis test.
Group I: postoperative methylprednisolone
Group II: preoperative methylprednisolone
Group III: control; Preop=preoperation; postop=postoperation.

An inflammatory cytokine that strongly correlates with pain; and the glucocorticoids turn out weaker than Nonsteroidal Anti-Inflammatory Drugs (NSAID) in reducing pain. To overcome these weaknesses in postoperative open cholecystectomy, glucocorticoids can be administered together with NSAIDs, notwithstanding the possibility of postoperative nausea and vomiting must be considered.

Conclusion
Preoperative intravenous injection of methylprednisolone reduced the IL-6 level significantly, but not significantly reduce PGE₂ level in open cholecystectomy surgery. The decreased values of IL-6 and PGE₂ postoperatively compared to those levels given preoperatively show a decrease in pain. Methylprednisolone administered intravenously before open cholecystectomy is able to decrease postoperative pain.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions         | $ | HSY |
|--------------------------------|---|-----|
| Research concept and design    | ✓ | ✓   |
| Collection and/or assembly of data | ✓ | -- |
| Data analysis and interpretation | ✓ | ✓   |
| Writing the article            | ✓ | ✓   |
| Critical revision of the article | -- | ✓   |
| Final approval of article      | ✓ | ✓   |
| Statistical analysis           | ✓ | ✓   |

Acknowledgement
We thank all operative-room-nurses and residents for their help during the study.

Publication history
EIC: D. John Doyle, Case Western Reserve University, USA.
Received: 04-Mar-2016 Final Revised: 19-Apr-2016
Accepted: 28-Apr-2016 Published: 06-May-2016

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Citation:
Suwarman S and Yuwono HS. Postoperative pain inhibition by preoperative methylprednisolone in open cholecystectomy with the assessment of IL-6 and PGE₂. J Anesthesiol Clin Sci. 2016; 5:3. http://dx.doi.org/10.7243/2049-9752-5-3