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Postoperative pain inhibition by preoperative methylprednisolone in open cholecystectomy with the assessment of IL-6 and PGE_2

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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. PGE_2 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 PGE_2.

Material and methods: The level of pain was assessed during the 1st hour of surgery, the 2^{nd}, 4^{th}, 8^{th}, 12^{th} and 24^{th} 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 24^{th} hour ($p=0.4999$). The postoperative PGE_2 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 PGE_2 level. Methylprednisolone administered intravenously before open cholecystectomy is able to decrease postoperative pain.

Keywords: Methylprednisolone, open cholecystectomy, IL-6, PGE_2

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 PGE_2 [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 PGE_2 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

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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 PGE_2 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-way anova 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

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

n=sample size; Sd=standard deviation; E=effect size; Zα and Zβ 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	1.000
Woman	4	4	4	--
Age (year) :				
Standard Dev.	42.6 (13.5)	52.8 (11.8)	54.2 (11.2)	0.085
Median	45	53	53	--
Range	22-68	30-72	38-73	--
Education :	2	4	5	0.710
High school	4	3	2	--
University	4	2	3	--
HARS:				
Median	3.5	3	3	0.016#
Rentang	3–4(a)	2–4(ab)	2–3(b)	--

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

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Tabel 2. IL-6 concentration of all Groups.

IL-6 (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)	0.044
Median	2.49	12.14	4.79	--
Range	0.95-28.05	1.61-140.0	0.39-68.7	--
1sthour postop (Sd)	65.30 (31.22)	22.13 (13.68)	61.04 (46.74)	0.013
Median	64.05	18.91	47.07	--
Range	21.61-106.28	5.89-50.33	5.30–140.0	--
4thhour postop (Sd)	18,46 (13.24)	13.62 (7.78)	39.48 (21.69)	0.002
Median	17.75	13.5	38.1	--
Range	1.10-49.82	3.6-24.9	4.36-78.07	--
24thhourpostop (Sd)	24.65 (22.04)	16.65 (15.21)	43.53 (39.10)	0.066
Median	16.78	10.66	29.53	--
Range	1.80-76.82	2.88–44.31	5.63-128.8	--

Results of F test (Anova), except 1st hour, 24th hour Kruskal-Wallis test.
Group I: methylprednisolone given postoperatively
Group II: methylprednisolone given preoperatively
Group III: Control Group; (Sd)=(Standard deviation)

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	0.001
Preop-4th hour postop	-12.55	21.85	-22.14	0.001
Preop-24th hour postop	-18.74	18.82	-26.19	0.003
1st hour-4th hour postop	46.84	8.51	21.56	0.010
1sthour-24th hour postop	40.65	5.47	17.52	0.113
4thhour-24th hour postop	-6.19	-3.03	-4.05	0.849

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

inhibition of cyclooxygenase which reduces the synthesis of prostaglandins, particularly PGE_2, in attenuating pain [5]. Thus, PGE_2 is an inflammatory cytokine that lowers pain threshold [5,6]. In the literature we found that in surgery the IL-6 triggers the release of PGE_2 from macrophages. PGE2 is potentially the most potent endogenous immunosuppressant, as it does suppress T-cell and macrophage responsiveness, it also induce IL-10 as a potent cytokine that deactivates monocytes [6,7]. In clinical cases the IL-6 levels correlate with Injury Severity Score (ISS) and the development of multiple organ failure, acute respiratory distress syndrome (ARDS) and septicaemia as well [7].

In this study, the postoperative production of IL-6 significantly decreased as a result of administrating methylprednisolone preoperatively, but it did not reduce the levels of PGE_2. The PGE_2 is an

Table 4. PGE_2 concentration.

PGE_2 (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)	0.179
Median	3994.8	2746.9	2593.6	--
Range	1635.2-5951.7	92.7-5309.2	259.7-5446.7	--
1sthour postop.(Sd)	2278.7 (1314.4)	1792.9 (1015.0)	2630.9 (1285.4)	0.316
Median	2345.6	1696.6	2734.0	--
Range	196.8-4306.7	120.8-3706.8	819.9-4254.1	--
4thhour postop. (Sd)	3077.3 (1432.7)	1570.4 (830.0)	2772.0 (1220.8)	0.032
Median	3260.6	1521.0	2303.6	--
Range	374.6-4629.3	362.1-2749.0	1635.2-4702.6	--
24thhourpostop. (Sd)	2767.8 (926.4)	1786.4 (1092.8)	2572.4 (1552.0)	0.182
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
GroupII: preoperative methylprednisolone
Group III: control; (Sd)=(Standard deviation)

Table 5. PGE_2.

PGE_2 (pg/ml)	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
1sthour - 24th hour postop	-489.1	6.5	58.5	0.727
4thhour - 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.

inflammatory cytokine that strongly correlates with pain; and the glucocorticoids turn out weaker than Nonsteroidal Anti-Inflammatory Drugs (NSAID) in reducing pain [8]. 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 PGE_2 level in open cholecystectomy surgery. The decreased values of IL-6 and PGE_2 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	S	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	✓	✓

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