Original Article

Age-related Differences in the Efficacy of Dexamethasone for Postoperative Analgesia in Patients undergoing Laparoscopic Cholecystectomy: A randomised controlled study

Cheol Lee[1], Jae-Yoon Chung[2], Myeongjong Lee[3]
[1]Department of Anesthesiology and Pain Medicine, Wonkwang University School of Medicine, Korea
[2]Department of Anesthesiology and Pain Medicine, Wonkwang University Sanbon Hospital, Korea
[3]Department of Anesthesiology and Pain Medicine, Konkuk University School of Medicine, Korea

Kuwait Medical Journal 2018; 50 (3): 282 - 287

ABSTRACT

Objective: This study aimed to investigate age-related differences in the effects of dexamethasone pre-treatment on pain intensity and morphine consumption in patients undergoing laparoscopic cholecystectomy.
Design: Randomized, prospective study
Setting: Operating room of a Wonkwang university hospital, South Korea
Subjects: Three hundred and eighty-eight patients undergoing laparoscopic cholecystectomy, 194 from a younger age group (18 - 45 years) and 194 from an older age group (≥ 65 years).
Intervention: The patients within each group were randomly allocated into younger (normal saline/dexamethasone: 97/97) and older (97/97) groups. They received either intravenous dexamethasone 0.1 mg/kg or normal saline 1 hour before anaesthesia induction.
Main outcome measures: The effect of dexamethasone on cumulative morphine-containing patient-controlled analgesia consumption, visual analogue scale scores for pain at 1, 2, 6, 12, and 24 hours after surgery, mean morphine consumption, and time to first rescue analgesia
Results: When dexamethasone was administered, both age groups had significantly less cumulative patient-controlled analgesia consumption, mean morphine consumption, and longer time to first rescue analgesia. These effects were of greater magnitude in the older than in the younger group. Visual analogue scales for pain at 1, 6, and 12 hours after surgery was significantly higher in the younger group.
Conclusion: The effects of dexamethasone on clinically relevant pain were greater in the older group, who experienced less post-operative pain. Further investigation regarding this association is warranted.

KEY WORDS: age, analgesia, dexamethasone, pain

INTRODUCTION

The evaluation and management of pain in elderly patients is a significant challenge for healthcare providers[1]. Evidence has shown that older patients report less pain after surgery and other interventional procedures[1,2]. The threshold for pain tends to be higher in older patients when the exposure to stimuli is brief, of lesser spatial extent, and at peripheral, cutaneous or visceral sites. Age-related increase in pain may be more apparent when stimuli are very intense and/or persist for longer periods[2,3].

Age and disease-related changes in physiology, diminished physiological reserves, and concurrent medications may alter the pharmacokinetics and pharmacodynamics of some analgesic medications and the techniques used in acute pain management. Functional, structural, and biochemical changes in nociceptive pathway have been reported in peripheral and central nervous systems in healthy older adults[4,5].

The anti-inflammatory effects of dexamethasone contribute to pain relief and amelioration of nausea and vomiting. However, it remains to be determined whether the efficacy of dexamethasone for reducing pain intensity and opioid consumption is affected by age-related differences[6,7]. This study aimed to investigate age-related differences in the effects of

Address correspondence to:
Myeongjong Lee, M.D, PhD, Department of Anesthesiology and Pain Medicine, Konkuk University School of Medicine, Konkuk University Chungju Hospital, 82, Gugwon-daero, Chungjusi, Chungbuk-do, Zipcode: 27376, Republic of Korea. Mob: +82-10-6416-2583, Fax: +82-43-840-8970, Email: gooddr21@naver.com

dexamethasone pre-treatment on pain intensity and analgesic consumption in patients undergoing laparoscopic cholecystectomy.

SUBJECTS AND METHODS

Ethical approval for this study (Registration No. 003549) was provided by the Institutional Review Board (IRB) of Wonkwang University Hospital, Iksan, Republic of Korea (Chairperson: Prof KH Yun) in January 2013. Written informed consent was obtained from all participants. The study was performed at Wonkwang University Hospital from February 2013 to December 2015. The study included 388 patients categorized into class I–II according to the American Society of Anesthesiologist (ASA) physical status; of these, 194 were younger (aged 18 - 45 years) and 194 were older (≥ 65 years) patients scheduled for laparoscopic cholecystectomy. Patients with hepatic and renal insufficiency, history of corticosteroid hypersensitivity, diabetes mellitus, previous gastric ulcers, cognitive impairment, or those receiving corticosteroids or immunosuppressive drugs and chronic opioids or other analgesics were excluded.

The patients were randomly allocated (sealed envelope) into a normal saline or dexamethasone group within each age group. There were 97 younger and 97 older patients each in normal saline and dexamethasone group. Patients in both groups received intravenous dexamethasone 0.1 mg/kg (5 mg/mL) or normal saline 1 hour before induction of anaesthesia.

On the day before surgery, all patients were taught how to use the visual analogue scale (VAS) and the patient-controlled analgesia (PCA) device. They were instructed to deliver analgesia on their own on feeling pain. We chose cognitively healthy patients who could comprehend the self-report pain assessment tools and the PCA technique in the acute pain setting.

Before the surgery, all patients were premedicated with intramuscular midazolam (2 – 3 mg). The patients were evaluated with pulse oximetry, automated blood pressure cuff, electrocardiogram, and end-tidal CO_2 monitors. Tympanic temperature was measured immediately before the induction of anaesthesia and again immediately before extubation.

For induction of anaesthesia, a slow (30 – 60 s) intravenous (IV) bolus of propofol (2 mg/kg) was administered. Tracheal intubation was facilitated with rocuronium (0.9 mg/kg) in all groups. Anesthesia was maintained with desflurane and a mixture of air and 50% oxygen. When additional desflurane was required, administration was started at an end-tidal concentration of 1 minimum alveolar concentration, and the concentration was adjusted by a 1% stepwise titration according to acceptable hemodynamic limits (mean arterial blood pressure between −30% and +15% and heart rate between −40% and +15%), and according to a target bispectral index (BIS) between 40 and 60.

Upon completion of the surgery, the neuromuscular blockade was reversed with pyridostigmine (0.2 mg/kg) and glycopyrrolate (0.008 mg/kg) when the train-of-four ratio had returned to 25%. The patients were extubated when BIS values reached 80 and spontaneous breathing was resumed.

The PCA mixture contained morphine (60 mg), ketorolac (150 mg), and ramosetron (0.6 mg) in 100 mL of saline. The device was set to deliver a basal infusion rate of 2 mL/h with bolus doses of 0.5 mL and a 15-min lockout period. Postoperative pain intensity was documented using a 100-mm linear VAS that consisted of a straight line, with the left end of the line representing no pain (0) and the right end of the line representing the worst pain (100). During post anaesthesia recovery, patients with VAS ≥ 40 received IV ketorolac (30 mg) and an additional dose (15 mg) if needed. Postoperative VAS on exertion was measured at 1, 6, 12, and 24 hours from the time of initial arrival at the post anaesthesia care unit (PACU).

The primary outcome was the effect of dexamethasone on cumulative, morphine-containing PCA consumption in both groups. The secondary measures of both groups were the effects of dexamethasone on VAS scores for pain at 1, 2, 6, 12, and 24 hours after surgery, mean morphine consumption adjusted for body weight, time to first rescue analgesia, ketorolac consumption in the PACU, postoperative nausea or vomiting (PONV), and pruritus in both groups. PONV was treated with IV ondansetron (4 mg).

Statistical analysis

Considering a power of 80% and an α-coefficient of 0.05 for effect of dexamethasone on cumulative, morphine-containing PCA consumption in both groups, sample size was calculated as 185 patients for each group. Assuming a 10% dropout rate, the final sample size was determined to be 194 patients per group (97 patients receiving dexamethasone and 97 receiving saline). The statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The results are presented as mean ± standard deviation (SD) or the number of patients (%). Means between groups were determined using independent t-test and categorical data were evaluated using Chi-square tests. Significance was defined as $p < 0.05$.

RESULTS

Eight of the 388 patients who were included in the study were excluded from the final analysis because of conversion to open surgery or re-exploration for

Table 1: Patients' characteristics

Variables	Younger group (n = 193)	Older group (n = 187)	p-value
Age (years)	41.1 ± 2.4	69.2 ± 2*	< 0.001
Sex (male/female)	98/95	93/94	NS
Body weight (kg)	62.6 ± 8.4	61.9 ± 6.2	NS
Duration of surgery (min)	58.2 ± 8.6	57.8 ± 8.8	NS
Time to first rescue analgesia (min)	35.3 ± 8.6	39.4 ± 9*	< 0.001
Ketorolac consumption (mg)	38 ± 7.5	35.5 ± 7.2*	0.001
Cumulative PCA consumption (ml)	65.3 ± 4.7	62.8 ± 5.9*	< 0.001
Mean morphine consumption (mg/kg)	1.06 ± 0.16	1.02 ± 0.14*	0.014
Pain intensity on exertion			
VAS 1 hour	43.9 ± 8.1	40.9 ± 10.2*	0.001
VAS 6 hours	34.5 ± 6.9	33 ± 7*	0.035
VAS 12 hours	26.8 ± 5.5	25.6 ± 6.1 *	0.039
VAS 24 hours	19.9 ± 5	19.6 ± 4.5	NS
Postoperative nausea or vomiting	32 (16.6)	16 (8.6)*	0.019
Pruritus	0	0	NS

Values are expressed as mean ± SD or number (%) of patients. VAS: visual analogue scale, PCA: patient-controlled analgesia; *p < 0.05 vs younger group; NS: not significant

postoperative bleeding. Of the 380 remaining patients, 193 were in younger age group and 187 were in older age group. There were no significant differences between the two groups with respect to sex, weight, and duration of surgery (Table 1).

Compared to the younger group, the older group had a significantly longer time to first rescue analgesia as well as a lower rescue analgesia (ketorolac) requirement, cumulative PCA consumption, and mean morphine consumption adjusted for body weight.

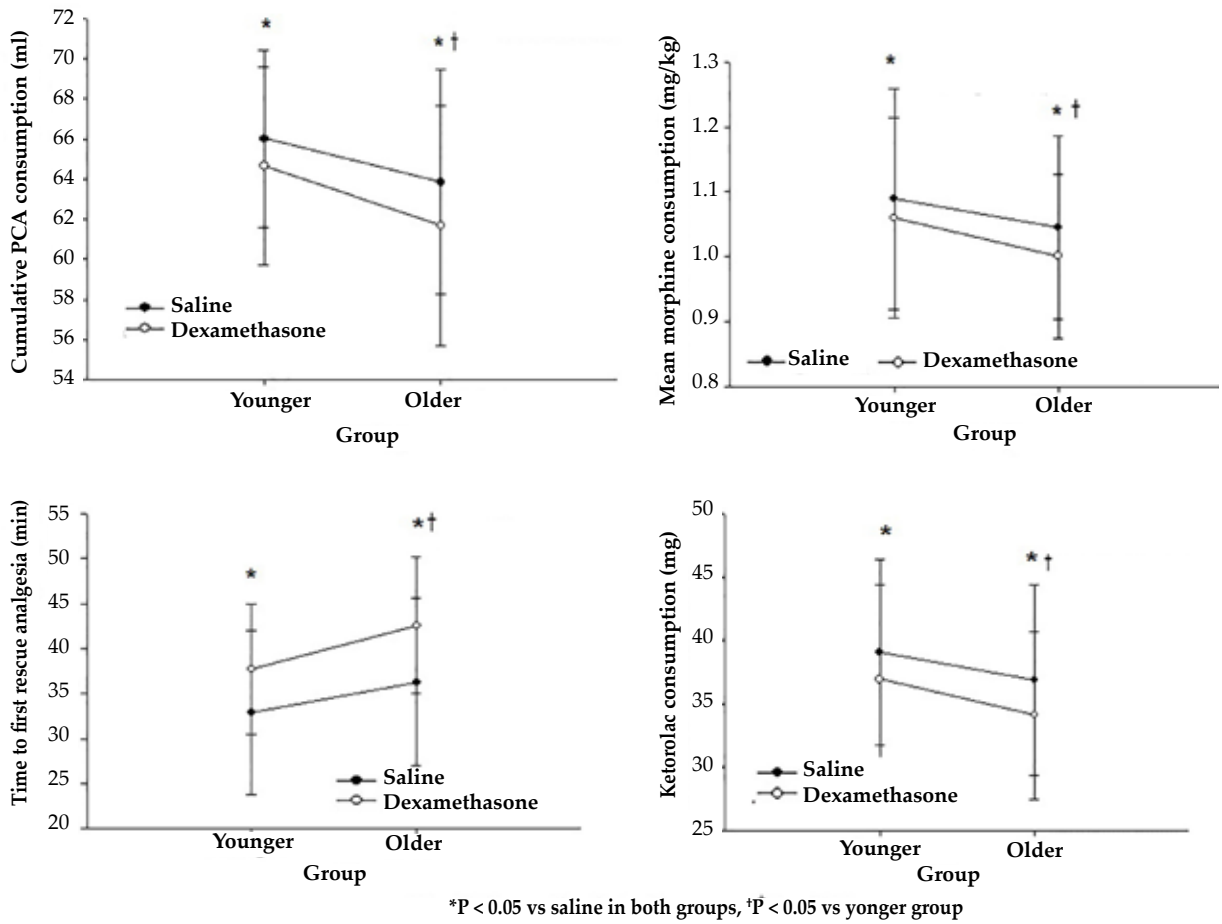


Fig 1: Clinically relevant pain

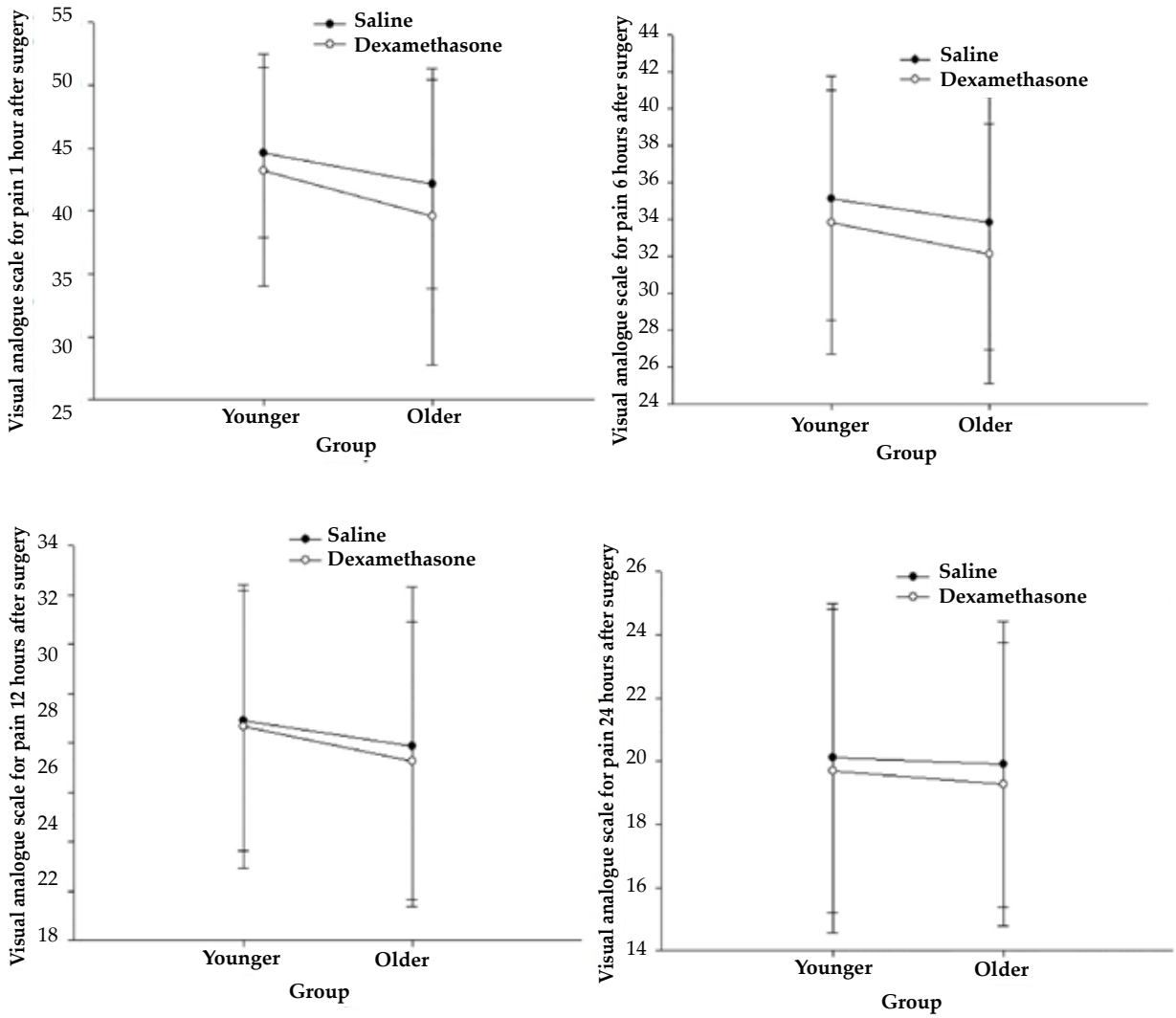


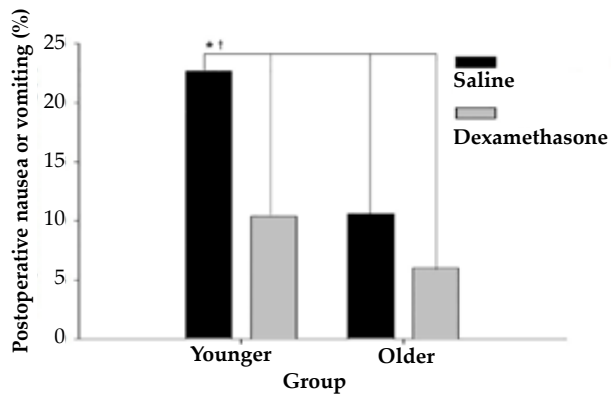
Fig 2: Pain intensity with visual analogue scale 24 hours after surgery

The older group also had lower VAS pain scores on exertion at 1, 6, and 12 hours postoperatively and a lower incidence of PONV (Table 1).

The use of dexamethasone in both age groups had significantly increased the time to first rescue analgesia and lowered the rescue analgesia (ketorolac) requirement, cumulative PCA consumption, and mean morphine consumption adjusted for body weight. These effects of dexamethasone on clinically relevant pain in the older group also appeared to be significantly greater than in the younger group (Fig 1).

The effect of dexamethasone in both groups on VAS for pain 24 hours after surgery was not significant, although these effects appeared to be greater in the older group than in the younger group (Fig 2).

Dexamethasone use in the younger group, rather than in the older group, showed a significant decrease in PONV. However, this effect in older group had a lesser degree of significance (Fig 3).



***P < 0.05 vs Dexamethasone in younger group, †P < 0.05 vs oldger group**

Fig 3: Postoperative nausea or vomiting

DISCUSSION

The present study showed that the older group experienced a lower intensity of pain, with a lesser amount of opioid consumption and a lower PONV than the younger group. The threshold for pain may

be increased in older patients when exposure to stimuli is brief, of lesser spatial extent, and at peripheral, cutaneous or visceral sites. Opioid requirements decrease with increasing patient age[3].

Age-related changes in the pharmacokinetics of many drugs used for pain management are common. This is primarily due to two factors: the progressive physiological decline that occurs with increasing age; and the increasing likelihood of concurrent disease. The changes that are of most significance to the pharmacokinetics of drugs used in acute pain management relate to renal function in particular, although other changes may also have some effect. Therefore, patients with hepatic or renal insufficiency were excluded in the present study. Age-related changes in pharmacodynamics also occur, although the underlying mechanisms are not fully understood. It appears that brain sensitivity to opioids increases by approximately 50% in older adults. However, it is not clear whether this difference is due to alterations in the number and/or function of opioid receptors in the central nervous system or other factors[4,5].

Age may influence the risk of PONV as emesis occurs less frequently in older patients. One of the factors responsible for decreased PONV in older adults could be the decrease in the dose of anesthetic agents administered[8-10].

A number of recent studies have investigated the potential analgesic benefit of dexamethasone and have yielded inconsistent findings, which are thought to be a result of the variability in the type of surgery, dexamethasone dose and timing, anaesthetic regimen, and type of postoperative rescue analgesic[6,7].

The results of the present study, with respect to the analgesic effects of dexamethasone, are consistent with those of previous clinical trials that have demonstrated the analgesic efficacy of dexamethasone. However, the previous studies have not taken into account potential age-related differences in dexamethasone efficacy.

The results of the present study revealed that the effects of dexamethasone on clinically relevant pain had a greater impact in the older group than the younger group (Fig 1), and the effect of dexamethasone on pain intensity for 24 hours in both groups was not statistically significant (Fig 2). These results may be due to the pharmacokinetic and pharmacodynamic changes of dexamethasone in the older group. A study reported that dexamethasone treatment led to an increase of glucocorticoid response element (GRE) binding activity in aged rats, whereas in young animals, GRE binding activity was decreased[11]. These changes in the brain induced by dexamethasone treatment is insufficient to explain our results. Dexamethasone has no short-term effects on pain sensitivity in terms of pain threshold, pain rating, and pain discrimination ability in healthy individuals[12].

In the present study, the younger group included women with menstrual cycles. Gonadal hormones are known to modulate pain intensity. A cyclical decrease in the pain threshold and an increase in morphine consumption have been observed in menstruating women, notably during the luteal phase. Studies involving healthy women volunteers have shown that women have greater pain sensitivity when they have low estrogen levels[13,14]. It is known that dexamethasone acts directly on the pituitary gland to suppress the action of estradiol and lowers circulating estrogens[15,16]. Taken together, in the present study, the effect of dexamethasone on clinically relevant pain in older group may mainly result from pharmacokinetics and pharmacodynamics rather than hormonal effect.

The present study showed that postoperative antiemetic effects of dexamethasone were greater in the younger group than in the older group. The effect of dexamethasone on PONV in the older group was minimal. The antiemetic mechanism of dexamethasone is unclear; it may be due to the release of endorphins that elevate mood and stimulate appetite. Additionally, it could be related to anti-inflammatory action within the gut that leads to reduction in the level of serotonin[17,18]. The opioid-sparing effect of the analgesic properties of dexamethasone may contribute to lower rates of PONV[19]. The apparent age-related difference in the efficacy of dexamethasone against PONV may be related to gonadal hormones. Estradiol may sensitize the chemoreceptor trigger zone and/or the vomiting center of the brain[14]. As mentioned above, pharmacokinetic and pharmacodynamic changes of dexamethasone in the older group may also affect its efficacy in PONV.

This study had some limitations. The individuals were grouped on the basis of only one parameter, *i.e.* age; however, biological "fitness" may be of more significance than chronological age. The physiological changes are progressive, but the rate of decline can be highly variable as physiological aging may or may not be concurrent with chronological aging. The results in the present study do not determine whether the observed changes are caused by the aging process or by other age-associated effects, including an increased presence of comorbid disease, bio-cultural cohort effects, or altered psychosocial influences.

The younger group in the present study included pre-menopausal women. We did not consider the hormonal state of the women or the stages of their menstrual cycles. Thus, this could be another possible, uncontrolled, confounding factor for the difference in the results.

CONCLUSION

The physiologic basis for age-related differences in pain response and analgesic efficacy is not completely understood. An improved understanding of the mechanisms underlying sex-related differences in pain perception and response to analgesic drugs should aid in formulating improved pain management strategies for postoperative patients. Although the observed age-related differences of dexamethasone in opioid effect may be clinically relevant, the lack of knowledge about other factors involved in the large variability of patient sensitivity to opioid analgesics sensitivity necessitates that practitioners customize their dose regimens on the basis of individual requirements.

ACKNOWLEDGMENT

This study was supported by Wonkwang University in 2016.

Conflicts of interest: None

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