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DEXMEDETOMIDINE ADDITION TO STANDARD CARE DURING LAPAROSCOPIC CHOLECYSTECTOMY

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Dexmedetomidine (DEX) is a highly selective α2 agonist with properties of sedation, analgesia and anxiolysis, making it an ideal anesthetic adjuvant. The aim of this study was to evaluate efficacy and safety of DEX infusion during laparoscopic cholecystectomy (LCE). The single-center, controlled study was carried at postgraduate department of surgery, anesthesiology and intensive care, Bogomolets National Medical University. Eligible participants were assigned to intervention (Group D; n=30) or control (Group C; n=30). Group D received dexmedetomidine infusion 0,5 mcg/kg/h from induction in anesthesia to extubation, group C (control) received normal saline infusion. DEX infusion was associated with lower incidence of severe postoperative pain and significantly lower time to first rescue analgesia. Also DEX infusin was assossiated with lower intraoperative fentanyl consumption, significantly lower time from end of surgery to extubation Intraoperative DEX infusion could be effective and safe to improve analgesia during LCE. DEX appears to significantly reduce the number of patients with severe postoperative pain, postoperative morphine consumption and time to first rescue analgesia.

Keywords: *postoperative pain, laparoscopic cholecystectomy, dexmedetomidine, randomized controlled trial.*

BACKGROUND AND AIM

Laparoscopic cholecystectomy (LCE) is usually associated with less pain compared to open approach, however postoperative pain is still the main complain after LCE and therefore often prolong hospital stay [1]. 36-63% of patients experience moderate abdominal and shoulder pain during 24-48 hours after LCE [2] and up to 13% of patients experience severe pain [3].

Opioids remain one of the main options for postoperative pain relief after LCE and most of patients require opioid analgesia [3, 4]. Nevertheless, opioids have side effects such as sedation, respiratory depression, nausea and vomiting, paralytic ileus, urinary retention, which may overweight analgesia efficacy, especially after abdominal surgery. It has been recommended to use opioids after abdominal surgery only when non-opioid drugs provide insufficient analgesia [1]. So there is a need to study and use of non-opioid pain medications after LCE.

Dexmedetomodine (DEX) provide sedative, sympatholytic and analgesic effect, so it could be used as an adjuvant to improve analgesia, hemodynamic response to intubation and pneumoperitoneum, decrease the number of opiod-assosiated adverse effects.

The aim of this study was to evaluate efficacy and safety of DEX infusion during LCE.

METHODS

The randomized, single-center, controlled study was carried out from May 2016 to June 2017 at department of surgery, anesthesiology and intensive care, Postgraduate Institute of Bogomolets National Medical University. Study design was approved by Ethical Committee at

Bogomolets National Medical University (approval code 56).

60 patients elected for LCE were included in the study. The inclusion criteria were: age between 18 and 79 years, either sex, ASA physical status I to II. The exclusion criteria were age outside the specified range, pregnancy or lactation, severe systemic disease (ASA III physical status), patients on b-blockers or calcium channel blockers.

After the primary patient assessment, eligible participants were assigned in a 1:1 ratio to either the intervention (Group D) or control (Group C) groups using random assignment in blocks of four. The randomization sequence was generated using a computer algorithm.

Group D received dexmedetomidine infusion 0,5 mcg/kg/h from induction in anesthesia to extubation, group C (control) received normal saline infusion. To prepare the infusion, dexmedetomidine 2ml containing 100mcg of the drug was diluted up to 50 ml with normal saline resulting in final concentration of 4mcg/kg. Dexmedetomidine or normal saline infusion was given through BBraun Space infusion pump.

After taking the patient to the operation room, vital signs monitor Philips, Bispectral Index (BIS) and ANI monitors were attached (pulse, heart rate, ECG, arterial pressure, oxygen saturation). Peripheral intravenous cannula was inserted for intravenous fluids and infusion pump (separate line). Patients did not receive premedication. Before induction they receive dexketoprofen 50mg IV and omeprazole 40mg.

Pre-oxygenation was performed for 2 min, induction in anesthesia – with propofol 2mg/kg IV and succinyl choline 1,5mg/kg IV. After intubation anesthesia was maintained with sevoflurane and atracurium bromide. The patients were ventilated with circle system with goal CO_2 35-45 mm Hg. BIS-monitor target was between 40 and 60, ANI monitor target was between 50 and 70. Anesthetics and drug infusion were stopped with the end of surgery.

The primary efficacy outcomes were number of patients with severe pain, time to first rescue analgesia and postoperative morphine consumption. Severe pain was estimated as verbal rating scale (VRS, [5] ≥7 during 30% or more time in first 48 hours after surgery. Time to first rescue analgesia was estimated as time from end of anesthesia to the time postoperatively when patient ask for analgesia or have VRS≥4. Injection morphine hydrochlorides 5mg subcutaneously was used as a rescue analgesic. NSAIDs (dexketoprofen 150mg per day) were prescribed routinely.

Secondary efficacy outcomes included:

- Intraoperative fentanyl consumption
- Time from end of surgery to extubation
- Lengths of intensive care unit (ICU) /general ward stay
- Postoperative pain in 3, 6, 12 and 24h after surgery

During first 48 hours after surgery patients in both groups were evaluated by the nursing stuff using the RASS scale for sedation, VRS (0 to 10) for pain assessment (every 2 hours or prior to rescue analgesia).

Safety was assessed by monitoring vital signs and recording adverse events. During anesthesia all patients receive continuous ECG, BIS, pulseoxymetry, capnography monitoring. AP was measured every 3-5min. Arterial blood gases were checked by doctor prescribtion. An adverse event was recorded if systolic blood pressure was <90 or >160 mmHg or if heart rate was <50 or >110 beats/min. Interventions for bradycardia, tachycardia, hypertension and hypotension comprised titration or interruption of study agent, or additional drug therapy. Postoperative sedation was recorded if patient had the level of sedation RASS ≤-3 during 24 hours after surgery.

Statistical analysis was performed using Statistica 8.0 and R software (StatSoft Inc., Tulsa, OK, USA). Categorical data are presented as proportions and continuous data as medians with 25-75% interquartile ranges (IQRs). Chi-square testing demonstrated that all of the study variables were discrete. To assess significance levels, a two-tailed Mann-Whitney U-test and Fisher's exact test were used. A p-value of <0.05 was considered significant.

Results and discussion. A total of 60 patients were randomized to the study group (n=30 per group). There were no significant differences between the study groups regarding demographic characteristics, comorbidities, ASA physical status.

Baseline characteristics of the study population are presented in Table 1.

Patients in both groups also have no differences in length of ICU stay – 14 [12-21] and 13 [12-20] hours; hospital stay – 72 [70-80] and 74 [72-82] hours in groups D and C respectively (p=).

The main outcomes of the study are presented in Table 2 and Pictures 1 and 2. As shown therein

Table 1. ***Demographic data and comorbidities***

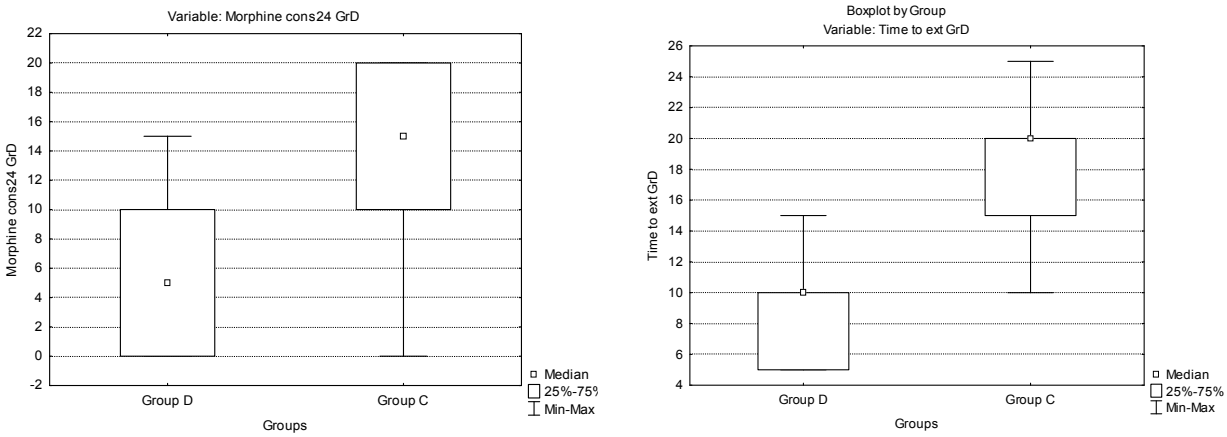
	Group D	Group C	P-value
Female, n (%)	27/30 (90)	26/30 (87)	p=0.3
Age, median (IQR)	55 [49 - 61]	53 [49-66]	p=0.5
Comorbidity:			
Arterial hypertension, n (%)	7/30 (23)	9/30 (30)	p=0.2
Diabetes Mellitus, n (%)	3/30 (10)	2/30 (7)	p=0.3
Chronic obstructive lung disease (COPD), n (%)	2/30 (7)	1/30 (4)	p=0.4
ASA physical status, median (IQR)	2 [1-2]	2 [1-2]	p=1
Obesity, n (%)	2/30 (7)	2/30 (7)	p=1

Value expressed as medians (InterQuartile Ranges 25 to 75), unless otherwise specified.

Table 2. ***Efficacy outcomes in study groups***

	Group D	Group C	P-value
Severe pain incidence, n (%)	1\30	7\30	P=0.04
Time to first rescue analgesia, min	180 (160-200)	80 (70-100)	p=0.001
Postoperative morphine consumption in 24 h, mg	5 (0 to 10)	15 (10 to 20)	p=0.001
Cumulative morphine consumption, mg	15 (10 to 25)	30 (20 to 30)	p=0.001
Time to extubation, min	10 (5-10)	20 (15-20)	p=0.001
Postoperative pain level 3 h after surgery, VRS	3 [3-4]	4 [4-5]	P=0,067
Postoperative pain level 6 h after surgery, VRS	4 [4-5]	5 [4-5]	P=0,08
Postoperative pain level 12 h after surgery, VRS	3 [3-3]	4 [4-5]	P=0,33
Postoperative pain level 24 h after surgery, VRS	4 [4-4]	4 [4-4]	P=0,72
Intraoperative fentanyl consumption, mg	0.5 (0.4 to 0.5)	0.6 (0.6 to 0.6)	P=0,001

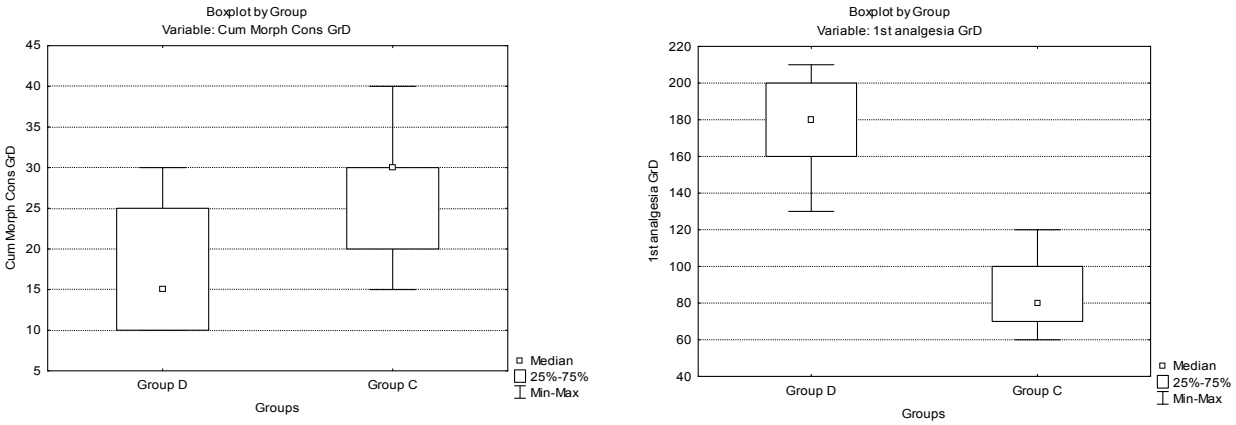
VRS – verbal rating scale. Value expressed as medians (InterQuartile Ranges 25 to 75), unless otherwise specified.



Picture 1. Morphine consumption during first 24h and cumulative during hospital stay.

intraoperative DEX infusion influenced many primary and secondary outcomes of the study, including opioids consumption, incidence of severe postoperative pain and opioid-related adverse events.

In this randomised controlled study, DEX infusion was associated with lower incidence of severe postoperative pain (odds ratio (OR) 9 CI 95% 1.1 to 77, p=0,04), significantly lower time to first rescue analgesia (p=0,001) and decrease in postoperative morphine consumption (p=0,001). On the other hand, the median pain intensity measured with NRS did not differ between group in 3, 6, 12 and 24h after surgery.



Picture 2. Time to extubation and time to first rescue analgesia in study groups.

Table 3. ***Adverse events rates in both groups***

	Group D	Group C	Odds ratio (CI 95%)	P-value
Hypotension, n (%)	8/30 (27)	4/30 (13)	2.2 (0.6 to 8)	p = 0,25
Hypertension, n (%)	5/30 (15)	22/30 (33)	13.8 (4 to 48)	p < 0.001
Tachycardia, n (%)	1/30 (3)	9/30 (30)	12.4 (1.5 to 106)	p = 0,02
Bradycardia, n (%)	6/30 (20)	2/30 (7)	3.5 (0.6 to 19)	P = 0,15
Postoperative sedation, n (%)	6/30 (15)	5/30 (20)	1.25 (0.3 to 5)	P = 0,7
Nausea/vomiting, n (%)	2/30 (6)	8/30 (27)	5 (1.1 to 26)	P = 0,05
Pruritus, n (%)	0/30	2/30 (6)	5 (0.2 to116)	P = 0,28

Opioid-sparing effect of DEX also was observed in other studies and meta-analysis [5, 7, 8]. At 3h after surgery the mean difference was -5.2mg (95% CI -5.79 to -4.61) for Bakhamees 2007 [7] and -3.65mg (95% CI -6.04 to -1.26) for Tufanogullari 2008 (5), respectively, 51% and 39% reduction. At 24h after surgery morphine consumption was reduced to 25-54% [7, 9]. This studies were estimated as low-quality evidence [8]. Analgesic efficacy of DEX on postoperative pain intensity was reported by very low-quality evidence, with a mean difference of -30 mm VAS (95% CI -38.25 to -21.75) [7]. Regarding the first request of rescue analgesia, the quality of evidence were also very low, and showed the increase in time for DEX, with a mean difference of 3.07 hours (95% CI 2.76 to 3.38) [9].

Also patients in group D had lower intraoperative fentanyl consumption (p=0,001), significantly lower time from end of surgery to extubation (p=0,001) and decrease incidence of persistent postsurgical pain (OR 4 CI 95% 1.1 to 19, p=0.049).

Regarding adverse events in this study, there was no difference in incidence of postoperative sedation (p=0.7), other studies showed the higher incidence of sedation within DEX groups with a mean difference in Ramsay Sedation Scale of 1.60 units (95% CI 1.49 to 1.71) [10, 11].

The incidence of postoperative nausea and vomiting (PONV) was reduced in group D (OR 5 CI 95% 1.1 to 26, p=0.005), which is similar with other study (5). Concerning hypotension and bradycardia incidence, there were no differences found in this study, however the incidence of hypertension was significantly higher in the group C (OR 13.8 CI 95% 4 to 48, p<0.0001). Similar results reported other authors [11], tachycardia and hypertension were registered in 7 and 6 patients of control group compared to 1 and 2 patients of DEX group.

The limitations of this study include the partially blinded design and the small sample size (n=70), which make it difficult to draw definitive conclusions.

Nevertheless, this trial supports use of intravenous dexmedetomidine as an analgesic

adjuvant for LCE and provides efficacy and safety outcomes. In the authors' opinion, we have enough data to consider dexmedetomidine as a valid adjuvant to intraoperative opioids during LCE. Although, there are no clear definition regarding cost-effectiveness in this case.

CONCLUSIONS

Intraoperative DEX infusion is effective and safe to improve analgesia during LCE. DEX appears to significantly reduce the number of patients with severe postoperative pain, post-operative morphine consumption and time to first rescue analgesia.

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ВИКОРИСТАННЯ ДЕКСМЕДЕТОМІДИНУ ЯК АД'ЮВАНТА АНАЛГЕЗІЇ В ЛАПАРОСКОПІЧНИХ ХОЛЕЦИСТЕКТОМІЯХ

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Дексмедетомідин – це α2-агоніст, який забезпечує седативний, симпатолітичний і знеболювальний ефекти, тому може бути використаний як ад'ювант для поліпшення аналгезії, гемодинамічної відповіді на інтубацію та пневмоперитонеум, зменшення опіоїд-асоційованих несприятливих ефектів. Метою даного дослідження була оцінка ефективності та безпечності інфузії дексмедетомідину під час лапароскопічних холецистектомій (ЛПХЕ). Одноцентрове, контрольоване дослідження проведено на кафедрі хірургії, анестезіології та інтенсивної терапії Інституту післядипломної освіти Національного медичного університету імені О.О. Богомольця. Пацієнтів, включених до дослідження, розподілили на дві групи: з інфузією дексмедетомідину (група D, n=30) і контрольну (група C; n=30). Пацієнти групи D отримували інфузію дексмедетомідину 0,5 мкг/кг/год. від індукції анестезії до екстубації, групи C (контрольної) – фізіологічний розчин. Інфузія дексмедетомідину забезпечувала меншу частоту серйозного післяопераційного болю та зменшення часу до першого знеболення за вимогою. Крім того, у пацієнтів групи D була тенденція до зниження інтраопераційного споживання фентанілу, значно менший час від закінчення операції до екстубації та зменшення частоти персистуючого післяопераційного болю. Інтраопераційна інфузія дексмедетомідину є ефективною та безпечною для поліпшення аналгезії під час ЛПХЕ. Дексмедетомідин може значно зменшити частку пацієнтів із тяжким післяопераційним болем, післяопераційне споживання морфіну та час до першого знеболення на вимогу.

Ключові слова: *післяопераційний біль, лапароскопічна холецистектомія, дексмедетомідин, рандомізоване контрольоване дослідження.*

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ИСПОЛЬЗОВАНИЕ ДЕКСМЕДЕТОМИДИНА КАК АДЪЮВАНТА АНАЛГЕЗИИ В ЛАПАРОСКОПИЧЕСКИХ ХОЛЕЦИСТЭКТОМИЯХ

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Дексмедетомидин – это α2-агонист, который обеспечивает седативный, симпатолитический и обезболивающий эффекты, поэтому может быть использован в качестве адъюванта для улучшения анальгезии, гемодинамического ответа на интубацию и пневмоперитонеум, уменьшение опиоид-

ассоциированных неблагоприятных эффектов. Целью данного исследования была оценка эффективности и безопасности инфузии дексмедетомидина в ходе лапароскопических холецистэктомий (ЛПХЕ). Одноцентровое, контролируемое исследование проведено на кафедре хирургии, анестезиологии и интенсивной терапии Института последипломного образования Национального медицинского университета имени А.А. Богомольца. Пациентов, включенных в исследование, распределили на две группы: с инфузией дексмедетомидина (группа D, n=30) и контрольную (группа С; n=30). Пациенты группы D получали инфузию дексмедетомидина 0,5 мкг/кг/ч. от индукции анестезии до экстубации, группы С (контрольной) – физиологический раствор. Инфузия дексмедетомидина обеспечивала меньшую частоту серьёзной послеоперационной боли и уменьшение времени до первого обезболивания по требованию. Кроме того, у пациентов группы D была тенденция к снижению интраоперационного потребления фентанила, значительно меньшее время от окончания операции до экстубации и уменьшение частоты персистирующей послеоперационной боли. Интраоперационная инфузия дексмедетомидина эффективная и безопасная для улучшения аналгезии в ходе ЛПХЕ. Дексмедетомидин может значительно уменьшить долю случаев с тяжелой послеоперационной болью, послеоперационное потребление морфина и время до первого обезболивания.

Ключевые слова: *послеоперационная боль, лапароскопическая холецистэктомия, дексмедетомидин, рандомизированное контролируемое исследование.*