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Is it Possible to Replace Fentanyl in Anesthesia for Minor Procedures?

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Abstract

Objectives

Evaluation of anesthetic and surgical outcome on using a combination of ketamine and lidocaine for induction of anesthesia and as intraoperative analgesia in comparison to fentanyl.

Patients and Methods

120 males assigned to undergo unilateral inguinal hernia repair requiring operative time less than 60 minutes were randomly divided into two groups: Group F received induction using fentanyl 1-2 ug/kg and intraoperative analgesia as a loading dose of fentanyl (1 µg/kg) over 1 minute followed by a continuous infusion of 0.3 µg/kg/h. Group L received induction by boluses of ketamine (0.5 mg/kg) and lidocaine (1 mg/kg) and intraoperative analgesia using a bolus dose of ketamine (0.5 mg/kg) and lidocaine infusion at a rate of 2 mg/kg/h.

Results

During the operative time, 28 and 79 patients had decreased mean arterial pressure by >20% and <20% of preoperative mean arterial pressure value, respectively with non-significant difference between both groups. Thirteen patients had an episode of increased mean arterial pressure up to <10% of preoperative mean arterial pressure with a significantly higher incidence in group L. At 30-min mean arterial pressure, both heart rate and mean arterial pressure measurements were significantly higher in patients of group L. Patients of group L had significantly faster post-anesthetic care unit discharge, but shorter time till the first request of rescue analgesia.

Conclusion

The applied intraoperative analgesia using ketamine and lidocaine infusion is a possible alternative for intraoperative fentanyl for short-duration surgical procedures. Usage of intraoperative ketamine/lidocaine infusion improved recovery parameters and reduced post-procedural complications with a short-duration postoperative hospital stay.

Keywords

Short-duration surgery; Intraoperative analgesia; Ketamine; Lidocaine; Fentanyl

Introduction

Pain was identified as the fifth vital sign and this leads to opioid over-prescription and misuse, with addiction reaching epidemic proportions [1] and constitute serious public health concern, so surgeons and specialists dealing with pain management must critically define optimal pain management [2]. Identification and management of pre-existing psychosocial factors, co-morbid pain entities and chronic opioid use significantly affect postoperative (PO) pain severity [3].

In addition to addiction, intense nociceptive stimulation and high-dose opioid administration can result in hyperalgesia and chronic postsurgical pain [4]. Other short term opioid-related adverse events include PO nausea and vomiting (PONV), constipation, itching, sedation, drowsiness, dizziness, and respiratory depression, may disturb PO recovery and extend the duration of PO hospital stay [5].

Balanced general anesthesia creates the anesthetic state through the administration of different drugs together so as to reduce doses used than if the drug was used alone though expanding the likelihood of its wanted effects and minimizing the likelihood of its unwanted effects (6).

Opioid-free anesthesia is a new paradigm that can deliver safe and stable anesthesia without intraoperative (IO) opioid to patients undergoing various surgical procedures [7] and as a part of Enhanced Recovery after Surgery (ERAS) pathway for lumbar spinal decompression [8], gynecological and breast surgeries [9] and bariatric surgery [10] to minimize perioperative opioid exposure without affecting pain control or recovery [8].

Ketamine, a phencyclidine intravenous anesthetic [11], isa racemicmixture consisting of (S)- and (R)-ketamine [12] that blocks N-methyl-d-aspartate (NMDA) receptors and hyperpolarization-activated, cyclic nucleotide-gated channels in the CNS [11]. Ketamine is largely used as an anesthetic, but it can also be used as an analgesic to manage chronic pain symptoms [13].

Local lidocaine anesthesia can influence local and systemic inflammatory response to surgery with reduction of plasma levels of pro-inflammatory cytokines with nociceptive action as interleukin-6, and tumor necrosis factor-α [14]. Intravenous (IV) lidocaine provided successful relieve of acute intractable renal colic unresponsive to standard therapy [15]. Moreover, IV lidocaine has analgesic effects that may lead to reduced PO opiate need, but this effect is still debated in various surgical populations [16].

The objective of the study is evaluation of anesthetic and surgical outcome, duration of PO analgesia on using combination of ketamine and lidocaine in comparison to fentanyl for induction and during maintenance of anesthesia

Patients and Methods

The study is a prospective comparative clinical trial. The protocol was approved by the Local Ethical Committee and was applied between January 2018 and July 2019 in Ain Shams University hospitals. All male patients assigned to undergo unilateral inguinal hernia repair requiring operative time of less than 60 minutes were eligible for evaluation for inclusion and exclusion criteria. This study is registered in clinicaltrials.gov number NCT03806374

All eligible patients underwent determination of demographic data, clinical evaluation to determine the American Society of Anesthesiologist (ASA) grade, baseline heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR) and peripheral oxygen saturation. Inclusion criteria included male patients aged 18-55 years, American society of anesthesiologists (ASA) grade of I or II, and were admitted to undergo open unilateral hernia repair requiring operative time of <60 minutes. Exclusion criteria included female patients, age out of the defined range, ASA grade >II, surgical indications requiring operative time >60 min as presence of obstructed or strangulated hernia, or other synchronous pathology that may require interference. Also, patients had allergy to anesthetic or drugs to be used, diabetes mellitus, hypertension, cardiac, renal, hepatic diseases, or refusal to sign the consent for participation were also excluded from the study.

Patients satisfying the consideration criteria were randomly designated into two equal groups. Each patient was asked to choose a sealed dark envelope containing a card carrying the group label. These envelops were previously prepared by an assistant who was blinded about the significance of the labels.

One-hundred and sixty one eligible patients were evaluated; forty one patients were excluded for not fulfilling the inclusion criteria; 7 patients had irreducible and 5 had manifestations of strangulated hernia, 6 patients were diabetics, 7 patients were hypertensive, 4 had chest diseases, 4 were hepatic patients and two patients had past history of allergy to volatile anesthetics. Also, 6 patients refused to participate in the study and were excluded. All surgeries were performed by a single team of surgeons.

One hundred and twenty patients who fulfilled the inclusion criteria were randomly divided into two equal groups: Group F included patients who will receive fentanyl during induction and maintenance of anesthesia and Group L included patients who will receive ketamine and lidocaine during induction and maintenance of anesthesia (Figure 1). Patients' enrolment data showed non-significant (p>0.05) difference between both groups (Table 1).

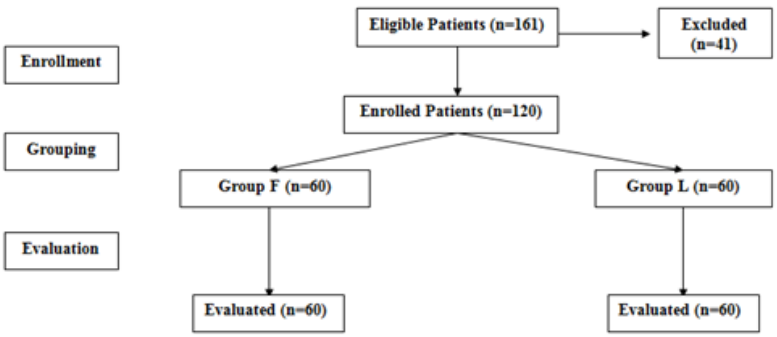

Figure 1: Flow Chart of the Study

Table (1): Enrolment Data of Patients of both Groups

Data		Group F	Group L	P value
Age (year)		38±9.1	36±7	0.352
Weight (kg)		81.8±6.7	84.4±7.4	0.595
Height (cm)		169.4±4	169.6±3.3	0.661
Body mass index (Kg/m^2)		28.5±2.6	29.4±2.8	0.492
ASA grade	I	49 (81.7%)	45 (75%)	0.375
	II	11 (18.3%)	15 (25%)	

Data are presented as mean±SD; numbers and percentages; group F received fentanyl infusion; Group L received ketamine and lidocaine infusion; P value indicates the significance of difference between both groups; P value >0.05 indicates non-significant difference between both groups

All patients were pre-medicated with midazolam (0.05 mg/kg), 2 min before induction of anesthesia. For patients of group F, anesthesia was induced using propofol 2 mg/kg, fentanyl 1-2 µg/kg, and cisatracurium 0.15 mg/kg. For patients of group L, anesthesia was induced using propofol 2 mg/kg, ketamine bolus injection of 0.5 mg/kg, a bolus injection of lidocaine in a dose of 1 mg/kg, and cisatracurium 0.15 mg/kg.

For both groups, after tracheal intubation, the lungs were ventilated with 100% O_2 in air using a semi-closed circle system for a tidal volume of 6-8 ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide ($paCO_2$) of 32-35 mmHg. Patients were continuously non-invasively monitored for MAP and HR and balanced anesthesia was maintained with sevoflurane MAC 1 in order to keep MAP with at ±20% of the preoperative measure and cisatracurium supplemental doses were given according to patient's physiological reaction to surgical stimuli.

Intraoperative analgesia was provided immediately after tracheal intubation; for patients of group F, IO analgesia was provided as a loading dose of fentanyl (1 µg/kg) over 1 minute followed by a continuous infusion of 0.3 µg/kg/h, while patients of group L had received a bolus dose of ketamine (0.5 mg/kg) and lidocaine infusion was started at rate of 2 mg/kg/h. Fentanyl and lidocaine infusions were adjusted according to need to reduce surgical stress effect on BP measures and were stopped prior to wound closure. At the end of surgery, residual neuromuscular blockade was reversed with intravenous injection of neostigmine 0.05 mg/kg with atropine 0.02 mg/kg IV, patients were extubated and transferred to the post-anesthetic care unit (PACU). At PACU, oxygen saturation was monitored using pulse oximetry and oxygen (6 L/min) was administrated via a face-mask if indicated. PACU discharge was dependent on Aldrete recovery score that ranges from 0 (comatose patients) to 10 (complete recovery), patients were discharged at score of ≥ 8 [17].

Severity of PO pain was assessed using an 11-point numeric rating scale (NRS) with numbers from 0 to 10 where 0 indicates no pain and 10 indicates worst pain imaginable [18]. PO pain was assessed at time of PACU discharge and 4-hourly till hospital discharge. Duration of PO analgesia was defined as time till first request of rescue analgesia that was supplied as IV parecoxib (20 mg diluted in 5 cc saline). Frequency of requests of rescue analgesia was also determined.

Primary outcome is the ability of IO analgesia to control MAP changes in reflex to surgical stress.

Secondary outcomes included

1. IO mean HR and MAP determined before and after intubation and every 15-min thereafter till extubation and at time of extubation.
2. Duration of surgery and time till fulfilling criteria for PACU discharge
3. Recurrence of demands of rescue analgesia, time till first ambulation, PO complications and PO hospital stay.

Statistical Analysis

With the assumption that postoperative analgesia will decline by 20 % in patients of Group L with confidence interval 95% and margin of errors 5%, the minimum number of patients needed was 55 patients in each group. Obtained data were presented as mean±SD, numbers, percentages and median. Results were analyzed using paired t-test for intra-group comparisons, One-way ANOVA Test for intergroup comparisons, Mann-Whitney test and Chi-square test (X^2 test) for non-parametric results. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Collectively, the difference in incidence of MAP deviation from preoperative MAP value was non-significant between both groups. During operative time, 28 patients (23.3%) had decreased MAP by >20% of the preoperative MAP; 16 patients (26.7%) in group F and 12 patients (20%) in group L with non-significantly (p=0.388) higher incidence among patients of group F. Thirteen patients (10.8%) had an episode of increased MAP, but the increase was by <10% of the preoperative MAP, 3 patients in group F and 10 patients (16.7%) in group L with significantly (p=0.0398) higher incidence in group L. The remaining 79 patients (65.8%) had decreased intraoperative MAP by <20% (Table 2).

Table (2): Extent of Intraoperative MAP change in Relation to Preoperative MAP in Patients of both Groups

Time	MAP change	Extent of change	Group F	Group L	P value
15-min	Decrease	by <10%	19 (31.7%)	21 (35%)	0.905
		10-<20%	37 (61.6%)	33(55%)	
		>20%	4 (6.7%)	4 (6.7%)	
	Increase	by <10%	0	2 (3.3%)	
		10-<20%	0	0	
30-min	Decrease	by <10%	17 (28.3%)	21 (35%)	0.326
		10-<20%	37 (61.7%)	32 (53.3%)	
		>20%	6 (10%)	3 (5%)	
	Increase	by <10%	0	4 (6.7%)	
		10-<20%	0	0	
45-min	Decrease	by <10%	24 (40%)	18 (30%)	0.205
		10-<20%	29 (48.3%)	31 (51.7%)	
		>20%	6 (10%)	5 (8.3%)	
	Increase	by <10%	1 (1.7%)	6 (10%)	
		10-<20%			

Data are presented as numbers & percentages; group F received fentanyl infusion; Group L received ketamine and lidocaine infusion; P value indicates the significance of difference between both groups; P value >0.05 indicates non-significant difference between both groups.

Hemodynamic measurements showed significant IO variability in patients of both groups in relation to their preoperative measurements with non-significant differences between both groups throughout operative time and at times of intubation and extubation, apart from measurements determined at 30-min IO when both HR and MAP measurements were significantly (0.0305 & 0.017, respectively) higher in patients of group L in comparison to patients of group F (Table 3)

Table (3): Intraoperative HR and MAP Measurements in Patients of both Groups

Variable	Time	Group F	Group L	P value
HR (beats/min)	Preoperative	82.3±3.9	81.3±4.8	0.074
	Before induction	76±4.2	75.5±4.1	0.513
	At time of intubation	88.3±3.9	88.7±4.8	0.618
	15-min IO	73.9±5.8	75.5±5.3	0.107
	30-min IO	72.2±4.8	74.3±5.6	0.0305
	45-min IO	74.1±6	74.2±4.5	0.946
	At time of extubation	83±5.7	82.3±4.3	0.461
MAP (mmHg)	Preoperative	90.3±4.9	91.6±6.5	0.228
	Before induction	80.6±5.1	81.9±6	0.212
	At time of intubation	91.3±5.4	93.1±5.8	0.097
	15-min IO	79.6±4.2	81.3±6.5	0.345
	30-min IO	79±5.1	81.4±5.6	0.017
	45-min IO	79.7±3.7	81±5.3	0.136
	At time of extubation	91.9±3.7	92.7±6.4	0.406

Data are presented as mean±SD; group F received fentanyl infusion; Group L received ketamine and lidocaine infusion; HR: Heart rate; MAP: Mean arterial pressure; IO: intraoperative; P value indicates the significance of difference between both groups; P value <0.05 indicates significant and >0.05 indicates non-significant difference between both groups

All surgeries were conducted uneventfully within a mean operative time of 44.9±6.2; range: 30-55 min with non-significant (p=0.291) difference between both groups. Patients of group L had fulfilled criteria for PACU discharge significantly (p=0.0049) faster than patients of group F. Fourteen patients did not require PO analgesia, 63 patients requested PO analgesia once, 40 patients requested PO analgesia two times and only 3 patients had three requests of PO analgesia with non-significant (p=0.762) difference between both groups. On the other hand, time till 1st request of rescue analgesia was significantly (p=0.034) longer with fentanyl than with lidocaine. However, the determined mean NRS scores, throughout PO hospital stay, showed non-significant (p=0.077) difference between both groups. Time till first ambulation was significantly (p=0.039) shorter in group L than in group F. The incidence of post-procedural complications was non-significantly (p=0.125) lower in group L than in group F and time till first ambulation and duration of PO hospital stay were significantly shorter in group L than in group F (Table 4).

Table (4): Operative and PO Data of Patients of both Groups

		Group F	Group L	P value
Operative time (min)		45.5±5.8	44.3±6.5	0.291
Time till PACU discharge (min)		18.9±4.7	16.6±4	0.0049
Number of requests of rescue analgesia	No	8 (13.3%)	6 (13.3%)	0.762
	One	33 (55%)	30 (50%)	
	Two	18 (30%)	22 (36.7%)	
	Three	1 (1.7%)	2 (3.3%)	
	Median	1 (IQR: 1-2)	1 (IQR: 1-2)	0.795
Time till first request of rescue analgesia (h)		4.7±1.4	4.1±1.4	0.034
PO pain NRS scores determined after PACU discharge	0-time	1.33±1	1.6±1.06	0.111
	2-h	2.22±1.15	2.27±1.25	0.819
	4-h	2.43±1.17	2.5±1.19	0.757
	6-h	2.15±1.13	2.3±1.12	0.468
	8-h	2.34±1.15	2.23±1.18	0.879
	10-h	2.62±1.33	3±1.8	0.624
	12-h	2±1.73	1.5±0.7	0.098
	Collective score	1.88±0.4	2±0.45	0.077
Time till first ambulation (min)		175.2±29.3	162.3±37.6	0.039
Post-procedure complications	Nausea	6 (10%)	2 (3.3%)	0.125
	Vomiting	2 (3.3%)	1 (1.7%)	
	Itching	3 (5%)	0	
	Agitation	1 (1.7%)	3 (5%)	
PO hospital stay (h)		8.5±1.35	8.1±1.1	0.029

Data are presented as mean±SD; numbers & percentages; group F received fentanyl infusion; Group L received ketamine and lidocaine infusion; PACU: Post-anesthetic care unit; NRS: Numeric rating scale; PO: Postoperative; P value indicates the significance of difference between both groups; P value <0.05 indicates significant and >0.05 indicates non-significant difference between both groups

Discussion

Surgical stress induced MAP deviation away from the preoperative measures to varied extents, however both infusions could ameliorate these pressor effects where 79 patients (65.8%) had decreased intraoperative MAP by <20% and 28 patients (23.3%) had decreased MAP by >20% of the preoperative MAP with non-significant difference between both groups.

These findings point to a favorable effect of regimen used for patients of group L, who received a bolus of ketamine and a lidocaine infusion (LI) and go in hand with Forster et al. [19] who found LI resulted in 50% reduction in propofol dose requirements during colonoscopy and Nakhli et al. [20] who reported reduction of volatile anesthesia and IO opioid consumption during renal surgery and concluded that IO lidocaine infusion could provide effective strategy especially in low and middle income countries. Also, Sakata et al. [21] reported that perioperative LI during bariatric surgery under sevoflurane anesthesia is feasible and easily accessible and allows reduction of IO sevoflurane and PO morphine consumption.

In support of the efficacy of LI, Kim et al. [22] found LI during anesthesia led to better quality of PO recovery measured by QoR-40 compared with placebo, while magnesium was found to be insufficient to induce any significant improvement. Also, Tran and Dhillon [23] reported significant relief of acute pain secondary to opioid-induced bowel dysfunction using LI and concluded that it may be an effective, but underutilized multimodal adjunct for nonsurgical pain conditions. Recently, Kheirabadi et al. [24] in a placebo-controlled study found that prophylactic administration of IV dexamethasone and lidocaine provided similar stable hemodynamic and respiratory conditions during surgical time with no significant difference in respiratory complications, pain score and vomiting incidence.

The reported effects of the used regimen could be attributed to the varied mechanism of analgesic action of ketamine and lidocaine. The reported analgesic and opioid sparing of lidocaine was previously attributed to inhibition of phosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II and protein expression levels in somatosensory cortical neurons [25] orto its inhibition of glutamate release from presynaptic terminals in spinal substantiagelatinosa neurons with concomitant hyper-polarization of postsynaptic neurons by membrane potential shifting leading to decreased excitability of spinal dorsal horn neurons [26]. Also, clinical trials suggested that perioperative LI may be a useful analgesic adjunct in enhanced recovery protocols due to its immuno-modulatory properties over surgical stress and so suggested its use in the context of multimodal analgesia [27].

Ketamine has myriad of molecular and cellular mechanisms responsible for its pharmacological functions including pain relief [28]. Ketamine is an antagonist for N-methyl-D-aspartate receptors [11], increases signaling through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors [12] and can regulate function of opioid receptors and sodium channels [13]. Additionally, ketamine exerts an anti-inflammatory effect through blocking of NMDA receptors [29].

Fentanyl infusion significantly reduced the hypertensive episodes than lidocaine (3 versus 10, respectively), but this was predicted effect owing to its documented effects on cardiac function [30] and was evidenced by the higher incidence of decreased MAP by >20% and by 10-20% with fentanyl more than with lidocaine.

Concerning PO outcome, both fentanyl and lidocaine infusions allowed reduction of number of requests of rescue analgesia with non-significantly lower frequency with fentanyl infusion, however patients received fentanyl infusion requested for PO analgesia after significantly longer PO time and this could be attributed to maintained plasma fentanyl concentration for about 60 min after a bolus injection and was higher if infusion was given after bolus injection [31].

Lidocaine infusion improved patients' outcome as manifested by the significantly reduced duration of PACU stay, time till first ambulation and duration of hospital stay. This could be attributed to the lower frequency of PONV and absence of sedation that may require prolonged hospital stay to fulfill criteria of home discharge. These data are in line with multiple studies evaluated perioperative IV lidocaine during varied surgical procedures and found IV lidocaine improved the immediate post-colonoscopy pain and fatigue [20], allows reduction of PO morphine consumption after bariatric surgery [22], reduced PONV and supported early recovery after laparoscopic gynecological surgery [32] and improved PO analgesia and bowel function after open radical cystectomy with urinary diversion [33].

Conclusion

The applied IO analgesia using ketamine and LI is a possible alternative for IO fentanyl for short-duration surgical procedures. Usage of IO ketamine/LI improved recovery parameters and reduced post-procedural complications with short-duration PO hospital stay. We recommend that randomized comparative multi-center studies are mandatory to standardize the used analgesic regimen

Limitations

The applied IO analgesic regimen was used for patients undergoing hernia repair to standardize the severity of surgical stress, however, the regimen to be standardized needs to be applied for variant surgical procedures.

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