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Research Article

Low dose ketorolac infusion improves postoperative analgesia combined with patient controlled fentanyl analgesia after living donor hepatectomy – Randomized controlled trial

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KEYWORDS

Ketorolac;
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Abstract *Background:* Hepatectomy elaborates significant post-operative pain. Opioids represent cornerstone for post-operative analgesia in such cases. This study examined the therapeutic effect and outcome of adding low dose ketorolac tromethamine infusion to PO intravenous patient controlled fentanyl analgesia IV-PCA.

Patients and methods: Sixty right lobe donors were randomized into either fentanyl or ketorolac groups (30 patients each). Patients in both groups received fentanyl (2 μg/ml) solution in normal saline as IV-PCA with background infusion in a rate adjusted to deliver 0.25 μg kg h^{-1} and boluses of 10 ml with a lock-out time of 20 min. They received 15 mg ketorolac IV bolus in ketorolac group and similar placebo injection in the control. Patients in both groups received a continuous intravenous infusion of 240 ml normal saline solution that is either free in the FENT group or containing 60 mg ketorolac in ketorolac group, adjusted to a rate of 0.2 ml kg h^{-1}. Visual analogue score

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(VAS) and hemodynamic profile were recorded at 1, 6, 12, 24, 36 and 48 h while laboratory results were recorded after 48 h and 7 days post-operatively.

Results: VAS was significantly lower in ketorolac group compared to fentanyl group from 6 to 36 h post-operatively while sedation score was significantly higher in fentanyl group compared to fentanyl–ketorolac group between 12 and 36 h post-operatively. Fentanyl consumption was significantly lower in ketorolac group at 24 (318.7 ± 66 vs 468.3 ± 79) and 48 (211.5 ± 59 vs 369.1 ± 68) h. Hemodynamic data and laboratory parameters were comparable in both groups. Nausea had a significantly higher incidence in FENT compared to KETR groups while other complications (vomiting and blood loss) were homogenous in both groups.

Conclusion: Adding ketorolac to IV PCA fentanyl improved the analgesic state and reduced the dose of fentanyl used without adding any side effects or risks to donors subjected to right lobe hepatectomy.

1. Introduction

Post-operative pain constitutes a major problem for patients after major abdominal surgery. Several modalities have been investigated; yet, consensus about an ideal protocol has never been reached. Liver resections mandates grave attention to post-operative analgesia protocol due to both large abdominal incision and the derangements on the drug pharmacokinetics ensued by major hepatic tissue resection. Epidural analgesia is a commonly used modality for post-operative pain management after liver resection [1]. However, the risk of epidural hematoma renders its use in those patients questionable and is often avoided [2].

Cywinski et al. used thoracic patient controlled epidural analgesia (PCEA) in right lobe resection for living liver donation and tumor resection. They found that patients subjected to right lobe liver resection for liver donation experienced significant post-operative pain compared to patients who had resection for malignancy. Additional factors were postulated to explain the predisposition of the right lobe liver donors to augmented post-operative pain perception [3]. Previous investigators demonstrated superiority of the epidurally administered opioids compared to intravenous rout using PCA technique in both [4,5]. Hence, Modifications in the IV PCA technique are required to enhance its activity to match the epidural rout.

Opioid analgesia, especially in high doses has many side effects as nausea, vomiting, pruritus, urinary retention, delayed bowel movement and respiratory depression which limit its use. The association of non-steroidal anti-inflammatory drugs (NSAIDs) with opioid is effective in postoperative analgesia, and can reduce the side effects due to opioid sparing effect [6]. Ketorolac tromethamine is a NSAID with a potent analgesic efficacy. While NSAIDs are always blamed for increasing bleeding tendency [7], lowering the dose of the NSAIDs may be of prime favorable impact on reducing this side effect. So, in this work, we tested the hypothesis that a low dose of ketorolac administered via IV infusion will synergistically add to the analgesic effect of PCA fentanyl without adding morbidity to patients after major hepatectomy. Pain assessed via visual analogue score was the primary outcome parameter in this trial.

2. Patients and methods

After approval of the relevant ethical committee and obtaining informed consent, 60 patients scheduled for right lobe hepatectomy for right lobe liver donation in Mansoura gastroenterology surgical centre – liver transplantation program were enrolled in this randomized double-blind controlled trial. Inclusion criteria included patients between 21 and 40 years old and right hepatectomy. Patients receiving non-steroidal anti-inflammatory drugs, anti-platelets or neuro-active or antipsychotic drugs and patients with history of recurrent hyperacidity or gastritis were excluded from the study. All patients were anaesthetized by the same anesthesia team using a standard anesthesia protocol. Anesthesia induction was achieved by intravenous injection of propofol 1 mg kg^{-1} and fentanyl 1 μg kg^{-1} and endotracheal intubation was facilitated by rocuronium bromide 0.3 mg kg^{-1}. Anesthesia was maintained by sevoflurane in oxygen/air mixture (40%) and fentanyl infusion 1 μg kg h^{-1} that was discontinued at peritoneal closure. Patients were extubated in the operating theater and transported to the intensive care unit (ICU). Upon admission to the ICU, patients were randomized into one of two groups based on the analgesic regimen using closed envelopes containing a randomly generated sequence of numbers pre allocated to the two groups. Fentanyl group (FENT) represented the control groups and fentanyl + Ketorolac group (KETR) represented the treatment group and each group included 30 patients who were all instructed about the proper use of the PCA pre-operatively and again at admission to the ICU. In both groups, analgesia was achieved via fentanyl using patient controlled intravenous analgesia (PCA). Fentanyl 500 μg were diluted in 250 cc normal saline to have a concentration of 2 μg ml and was attached to PCA pump (LifeCare 4100 PCA II system, by Abbott medical systems, USA). Background infusion was adjusted at a dose of 0.25 μg kg h^{-1} commenced while the Push up bolus doses were adjusted to give 10 mls of the solution (20 μg) and lock-out interval was adjusted to 20 min. Another solution was prepared containing either 240 ml normal saline (placebo) or 60 mg of ketorolac in 240 ml saline (concentration of 250 μg ml) and the solution was infused continuously in a rate of 0.2 ml kg h^{-1} to deliver a dose of 50 μg kg h^{-1} of ketorolac. Patients in fentanyl group (FENT) received a single injection of 100 ml normal saline (placebo) intravenously over 30 min while in ketorolac group (KETR), patients received a single injection of 15 mg of ketorolac in 100 ml normal saline intravenously over 30 min. All infusions continued for 48 h. Both the patient and the physician assessing the pain score and hemodynamic data were unaware of the infused solutions. Visual analogue score (VAS) was assessed at 1, 6, 12, 24, 36 and 48 h (at rest) using a standard VAS ruler (0–10) and sedation was simultaneously assessed by RAMSY(8) sedation score (6 points score)

by the attending intensive care resident. Nausea and vomiting were assessed on a binary scale (Present/Absent) and were presented as incidence (%). Hemodynamic data were recorded at the same time points with VAS. Laboratory assessment was performed in the morning of the third and seventh post-operative days. Bleeding time was assessed using Duke's technique and blood loss was calculated from the abdominal drains plus any significant soaking of the dressing. Total amount of fentanyl given was recorded at 24 and 48 h. The primary outcome objective of this trial is the 24th hour VAS while secondary objectives included daily fentanyl doses, degree of analgesia, hemodynamic profile, laboratory profiles and complications.

2.1. Statistical analysis

The primary outcome objective in this trial was VAS. For sample size determination, the 24th hour value was used for effect size. A priori power study was performed to detect an effect size of 20% and alpha error or 0.05% to acquire 90% power. 26 cases per group were required to achieve the designated power yet, 30 patients were enrolled in every group for compensating for probable withdrawals and disqualifications. Continuous data were tested for normality using kolmogrove–smirnove test and all exhibited normal distribution and were presented as mean ± SD. Differences between groups were tested using two-tailed independent sample t test (equal variance assumed). Interval data and total fentanyl doses were tested for significant difference between groups using Mann-Whitney U test. Incidence of nausea and vomiting was compared using Chi square. Statistical significance was assumed when P is less than or equal to 0.05 and analysis was performed using Statistical package for social sciences (SPSS) ver 14.USA.

3. Results

The study recruited 60 patients who were randomized into either fentanyl or fentanyl + ketorolac groups. 30 patients were enrolled in each group. Out of them 29 patients completed the protocol in FENT group while 1 patient was excluded during the study period due to revision operation (patient 8). In KETR group, 28 patients completed the protocol while one case was excluded due to surgical revision and another case for protocol violation (Unblinding) (patient 32) (Fig. 1). Neither patient characteristics nor operative data showed any significant differences between the studied groups (Table 1). Day three hemoglobin, ICU blood loss and ICU stay were homogenous among both groups (Table 1). Table 2 demonstrates MAP, HR and RR for the studied groups and showed no significant differences in these parameters among patients in both groups. Visual analogue score was significantly lower in KETR group compared to similar values in FENT group starting from 6 h reading until 36 h readings while sedation score was significantly higher in the FENT group compared to the KETR group from 12 to 36 h post-operatively (Fig. 2). Meanwhile, the Daily doses of fentanyl were significantly lower in KETR group compared to FENT group at 24 h (318.7 ± 66 μg vs 468.3 ± 79 μg, $P = 0.013$, CI = (11.50–92.13) and 48 h (211.5 ± 59 μg vs 369.1 ± 68 μg, $P = 0.001$, CI = (70.45–112.56) (Fig. 3). Outcome parameters included liver functions, renal functions and coagulation profile. Neither of these outcome parameters

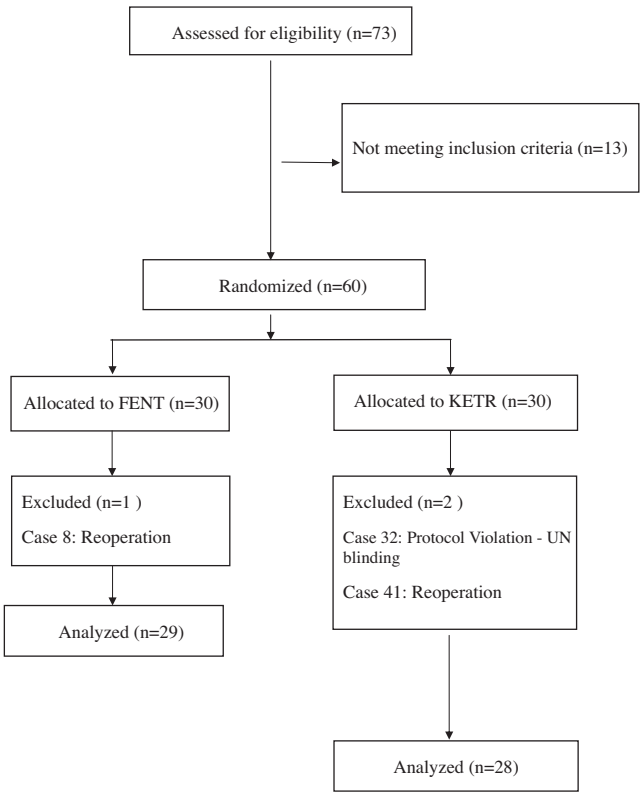

Figure 1 CONSORT chart.

demonstrated significant difference between both groups both at 3rd and 7th PO days (Table 3). Nausea was significantly more frequent in the FENT group compared to KETR group (58.62 vs 21.42, $P = 0.021$) while vomiting, and blood loss did not differ significantly among the studies groups (Table 4).

4. Discussion

This trial evaluated the analgesic efficacy of adding low dose of ketorolac tromethamine continuous intravenous infusion to IV PCA fentanyl after right lobe donor hepatectomy and found that the addition of ketorolac to IV PCA fantanyl achieved better analgesia, better patients alertness and reduced the incidence of nausea in this sensitive patient group without adding any morbidity.

Intravenous patient controlled analgesia give good analgesia and patient satisfaction by allowing the patients to control their pain [9,10]. In this study, patients receiving both IV PCA fentanyl and IV infusion of Ketorolac experienced less pain expressed as a significantly lower visual analogue score compared to patients receiving IV PCA fentanyl only from 6 to 36 h postoperatively. IV-PCA using both opioids and NSAIDs is a common method for acute post-operative pain management. The synergism between NSAIDs working primarily via modulation of arachidonic acid cascade at peripheral sites with opioids that act mainly centrally on specific receptors is effective in different types of surgery [11,12]. Na et al concluded that IV-PCA with fentanyl and ketorolac provides satisfactory and safe posto-perative analgesia after craniotomy [13].

In our trial, we investigated right lobe liver donors who share common characteristic features that influence drug phar-

Table 1 Patients characteristics: Data are in mean ± SD, number (range) or ratio.

	FENT group	KETR group	*P* value
Age (years)	28.24 ± 5.2	30.18 ± 4.9	0.166
Sex (M/F)	24/5	26/2	0.348
BMI	21.2 ± 2.1	22.3 ± 1.9	0.094
Operative duration (min)	273.6 ± 56	301.7 ± 69	0.231
Intraoperative fentanyl (Ug)	463 ± 105	415 ± 97	0.524
ICU stay number (Range)	2(2–3)	2(2–3)	0.92
Platelets	303.3 ± 56.3	295.5 ± 45.9	0.073
Admission Hg	12.45 ± 1.1	12.3 ± 1.3	0.064
Day 3 Hg	11.8 ± 1.1	11.4 ± 1.2	0.311
IO blood product transfusion	0	0	–
Remaining liver volume (%)	37.4 ± 3.1	36.3 ± 2.9	0.427

BMI = body mass index, Hg = hemoglobin and IO = intra-operative.

Table 2 Hemodynamic data of FENT group (n = 29) and KETR group (n = 28): Data are in mean ± SD.

	Heart rate		*P*	Mean arterial pressure		*P*	Respiratory rate		*P*
	FENT group	KETR group		FENT group	KETR group		FENT group	KETR group	
1 h PO	87.3 ± 4.5	85.5 ± 6.8	0.214	85.5 ± 3.8	86.3 ± 2.8	0.344	20 ± 3.1	21 ± 3.3	0.748
6 h PO	85.3 ± 4.2	82.3 ± 6.1	0.425	90.8 ± 4.8	93.3 ± 5.6	0.056	19.2 ± 2.5	20.2 ± 1.0	0.453
12 PO	81.7 ± 4.1	80.3 ± 3.7	0.061	89.8 ± 5.2	88.7 ± 5.3	0.741	17.3 ± 1.9	19.0 ± 2.5	0.081
24 h PO	78.8 ± 4.7	79.2 ± 5.4	0.121	82.5 ± 5.7	86.2 ± 5.5	0.455	15.3 ± 1.6	14.8 ± 1.9	0.132
36 h PO	79.5 ± 5.3	80.3 ± 4.5	0.072	88.2 ± 4.8	87.2 ± 5.0	0.059	14.3 ± 1	14.2 ± 1.2	0.063
48 h PO	78.5 ± 3.9	79.0 ± 3.5	0.278	79.8 ± 1.5	82.2 ± 6.1	0.521	14.0 ± 1.8	13.5 ± 1.5	0.547

PO = Post-operative.

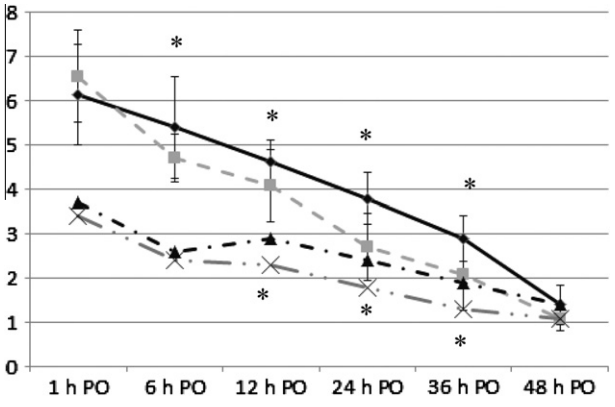

Figure 2 Visual analogue score and sedation score for the studied groups. *Significant compared to Fentanyl group.

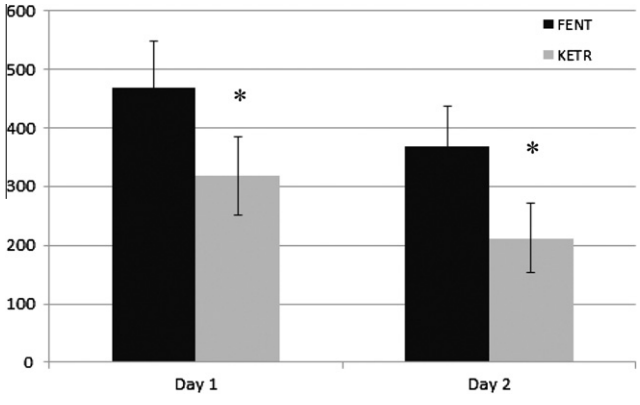

Figure 3 Fentanyl used in the study groups during the study period.*Significant compared to Fentanyl group.

macokinetics in general. First, around 60–65% of their liver is usually resected reducing their metabolic capacity of the liver especially for drugs which are primarily metabolized through the liver like Ketorolac [14]. Second, those patients almost always receive no blood product transfusion for fear of transfusion acquired infections, hence, blood loss is always replaced by fluids reducing the circulating quantity of plasma proteins and diluting the already existing amount. Drugs that are extensively pound to plasma proteins like ketorolac will subsequently have a more free active percentage of the drug in the circulation [14]. These two elements justified the use of a lower dose of ketorolac in this patient category compared to the standard dosage recommended in other post-operative settings [15] Our findings supported these assumptions since an appreciably low dose of ketorolac infusion (50 μg kg h^{-1}) could achieve the desired analgesic target. Both groups exhibited a difference between them after 6 h from starting the infusion, a time that was required to build up a sufficient trough level of ketorolac in the plasma after a reduced bolus dose of 15 mg given initially to this group that could not initiate a statistically significant difference with the control group in this early phase with maximum pain. Meanwhile, at 48 h, patients in both groups had a satisfactory analgesia. A finding that points mainly to the build up of a sufficient analgesic barrier by fentanyl alone fortified by the chronologically induced reduction of pain intensity after 48 h from surgery.

Table 3 Outcome parameters (liver functions, coagulation profile, renal functions and blood loss)data of FENT group (n = 29) and KETR group (n = 28) at post-operative day 3 and day 7: Data are in mean ± SD.

	FENT group	KETR group	Difference (95% CI)
Day 3 Lab. results			
S. Bilirubin	2.05 ± 0.76	1.85 ± 0.50	0.20 (−0.63 to 1.03)
ALT	187.8 ± 85.92	173.7 ± 32.8	14.17 (−69.49 to 97.83)
PC	66.0 ± 7.9	68.5 ± 8.1	−2.5 (−12.77 to 7.77)
INR	1.6 ± 0.37	1.6 ± 0.23	−0.02 (−0.41 to 0.38)
Bleeding time	3.2 ± 1.4	3.5 ± 1.9	−0.30 (−1.10 to 0.96)
Factor V	57.0 ± 7.3	61.2 ± 9.6	−4.20 (−15.10 to 1.23)
aPTT	46.5 ± 7.0	47.5 ± 6.2	−1.0 (−9.54 to 7.44)
S. Createnine	1.0 ± 0.14	0.95 ± 0.16	0.05 (−0.15 to 0.25)
Blood urea	28.0 ± 3.58	26.5 ± 5.43	1.50 (−4.42 to 7.24)
Day 7 Lab. results			
S. Bilirubin	1.17 ± 0.12	1.7 ± 0.23	0.00 (−0.23 to 0.24)
ALT	69.7 ± 32.4	58.2 ± 26.8	11.5 (−21.4 to 16.8)
PC	83.5 ± 6.7	85.4 ± 6.0	−1.83 (−9.9 to 6.33)
INR	1.17 ± 0.08	1.06 ± 0.08	−0.01 (−0.11 to 0.12)
Bleeding time	2.8 ± 1.0	3.0 ± 1.2	−0.20 (−0.970 to 0.78)
Factor V	91.0 ± 3.5	90.8 ± 2.9	0.16 (−3.99 to 4.33)
aPTT	42.8 ± 10.2	44.3 ± 8.9	−1.4 (−7.63 to 6.96)
S. Createnine	0.87 ± 0.18	0.71 ± 0.37	0.16 (−0.22 to 0.53)
Blood urea	20.83 ± 2.48	23.33 ± 4.23	−2.50 (−6.95 to 1.96)

ALT = alanine aminotransferase, PC = prothrombine concentration, INR = international normalization ratio and aPTT = activated partial thromboplastine time.

Table 4 Complications of FENT group (n = 29) and KETR group (n = 28).

	FENT	KETR	P value
Nausea (%)	58.62	21.42*	0.021
Vomiting (%)	7.14	10.34	0.415
Blood loss (ml)	301.7 ± 26.4	268.3 ± 0.24	0.113

* $P < 0.05$ compared to the control group.

Munro et al, in their trial, were in agreement with our findings regarding the synergistic effects of adding sub-standard dose of ketorolac to opioid analgesic were they recorded a lower pain score in the ketorolac treatment group and also, lower opioid consumption (20%) in both post-operative day 1 and day 2 compared to opioid only control group [16]. Similar results was achieved by Kim and his collogues using remifentanil and ketorolac [17].

In this work, we assessed sedation in this trial using the 6 points Ramsey sedation score [8]. Patients in KETR group exhibited better (lower) sedation score compared to patients in FENT group between 12 and 36 h post-operatively. The significantly lower overall daily dose of fentanyl administered in the KETR group compared to the FENT group by 31.9% in the first 24 h and by 42.7 in the second 24 h could justify the higher sedation score in the FENT group. Previous investigators had similar results with the addition of ketorolac to their post-operative opioid based analgesia. (REF KIM) The lack of significant difference in the sedation score between both groups at the end of the study (48 h) is attributed to the very low sedation score achieved in both of them with patients requiring less fantanyl in both groups compared to the first 24.

NSAIDs are accused by increasing blood loss duo to inhibition of platelet aggregation [18]. Yet, the results are conflicting among different subsets of NSAIDs [19]. Previous investigators reported an increase in the bleeding tendency in their trials using ketorolac [7,20]. Yet, in these two trials, a different population (pediatric) was used, the type of operation (tonsillectomy) where the incidence of bleeding is increased by 3.5 times in ENT surgery compared to other surgical sites [21] and the dose of ketorolac given in both studies (1 mg kg) were the complications of ketorolac were previously demonstrated to be dose-dependent [22] may have participate in these results that are contradictory to our findings in this trial were the addition of ketorolac to IV PCA fentanyl did not induce any significant differences from the control group in bleeding time, transfusion requirements or blood loss. Liver resection results in decrease in the concentration of clothing factors due to transient insufficiency of the remaining liver to synthesize new factors, factor consumption and operative fibrinolysis [23,24]. However, this effect is time dependant and may not be effective during the first 24–48 h post-operatively especially with donor hepatectomy due to the supreme quality of the donor liver documented through the extensive pre-transplant work up in our center including liver biopsy.

The incidence of nausea in our trial was significantly lower in the kETR group compared to the control group. These results were in agreement with previous work on abdominal surgery with reported reduction of the incidence of nausea in ketorolac treated patients [12]. Previous studies reported an anti-emmitc effect of ketorolac in different post-operative settings [25,26].

One of the study limitations was the restriction of the cohort to a limited age group (21–40) which is the age for acceptance for right lobe liver donation in our program, hence, we cannot recommend extrapolation of our findings to different age groups. Also, the excellent quality of the donor livers may have played a major role in the results of our study that may not be safely achieved if applied to patients with diseased liver sub-

jected to major hepatectomy. We could conclude that low dose iv infusion Ketorolac tromethamine augmented the post-operative analgesic effect of IV PCA fentanyl without any added morbidity to patients subjected to right lobe liver hepatectomy for liver donation.

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