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# The Comparison of the Analgesic Effect of Intravenous Acetaminophen with Fentanyl in Thoracic and Abdominal Surgeries of Newborns

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## *Abstract*

### *Background*

The use of opioid drugs for controlling pain during and after surgery is a common but complicated procedure in neonatal anesthesia. This study compared the analgesic effect of acetaminophen with fentanyl after abdominal and chest surgery in Iranian newborns.

### *Materials and Methods*

This randomized, double-blind clinical trial was conducted in two hospitals; in the NICU of Shahid Motahari hospital in Urmia and Namazi hospital in Shiraz, Iran. Sixty-six patients were randomized sequentially and assigned in two groups. One group of patients received acetaminophen dose of 10 mg/kg every six hours, and another group received fentanyl 6 µg/Kg every six hours for 48 hours (9 doses). For all patients, pain was assessed using the "Neonatal Infant Pain Scale (NIPS)" at first time, 6, 12, 18, 24, 30, 36, 42 and 48 hours (9 measurements). If necessary, fentanyl 1 µg/Kg was injected to the patients. Finally, all the information was recorded and analyzed using SPSS software (version 21.0).

### *Results*

The mean age of the fentanyl group was 16.79 ± 15.57 days and 16.67 ± 15.77 days in the acetaminophen group (P>0.05). The mean weight in the fentanyl group was 3460 ± 737 gr and in the acetaminophen group was 3228.548 ± 32.28 gr (P>0.05). Results showed that the mean scores of pain in all periods of time were not significantly different between the two groups (P>0.05). No drug complications were seen in the acetaminophen group.

### *Conclusion*

Based on the results, mean score of pain in fentanyl and acetaminophen groups was not statistically significant. Acetaminophen did not control pain as well as fentanyl in neonatal surgeries.

***Key Words:*** Acetaminophen, Analgesia, Fentanyl, Newborn, Surgery.

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## 1- INTRODUCTION

According to the World Health Organization (WHO), "pain" is an unpleasant and sensory experience, with potential or actual damage to the tissue (1). Post-operative pain control reduces the mortality rate in the infant. One of the main problems of neonates in post-operation period is pain that usually presents in three main manifestations: crying, body movements and facial expressions (2). Reducing the amount of pain, significantly contributes to improved clinical outcomes of newborns in post-operation period (3). There is evidence that infants are able to form tactic memory of pain. Ignoring the reduction of pain of the infant can lead to negative consequences on their behavior. Behavioral and neurological studies indicate that premature infants who experience frequent painful procedures and severe stimuli do not respond to painful stimuli at 18 months of age. The response to pain during vaccination at 2, 4 and 6 months among infants who have been circumcised in a neonatal period without analgesia are considerably more likely than the baby boy who has not been circumcised or who has received sufficient analgesic during circumcision (4).

Other complications of pain in newborn include hypoxia, hyperglycaemia, and respiratory distress. Various drug categories are used to relieve pain in newborn, including opioid analgesics, local analgesics, sedatives, and non-steroidal anti-inflammatory drugs (NSAIDs) (2, 4). One of the most commonly used opioid drugs is morphine. Morphine is used to relieve acute, moderate to severe pain during and after surgery. Infants and especially preterm infants are very sensitive to morphine. Some studies have pointed to morphine side effects such as apnea, hypotension and urinary retention, defects in respiratory mechanisms and bronchospasm (5, 6). Fentanyl is also an opioid analgesic and a synthetic opioid that is 50 to 100 times more potent than morphine. It can be given as a slow intravenous injection every 2 to 4 hours or as an infusion continuously. Withdrawal syndrome and drug tolerance may occur after continuous infusion for 5 days or more. The use of fentanyl decreases heart rate and reduces the score of behavioral stress and pain, compared with placebo. However, neonates under mechanical ventilation who receive fentanyl need more rapid ventilation and also have a higher inspiratory pressure within 24 h (7). Acetaminophen is a Cyclo oxygenase (COX) inhibitor and antipyretic, which is also used as an analgesic. In order to create an analgesic effect, its plasma concentration should be 10-20 mg/ml (8). Studies show that acetaminophen is well tolerated in newborn and does not increase liver enzymes; it has no effect on blood pressure and can have a limited effect on heart rate (6, 9). The use of these opioid drugs is associated with complications such as nausea, vomiting, sedation and respiratory depression, and the concomitant prescription of non-opioid analgesic is a useful way to reduce the use of opioids and minimize complications (10). One of the studies conducted in this area suggests that the use of an alternating dose of injectable acetaminophen following surgery would reduce the morphine dose by about 66% during the 48 h after surgery (11).

However, in another study in the Netherlands, in which researchers compared rectal acetaminophen and morphine, there was no significant difference in the cumulative amount of morphine received in the two groups of acetaminophen and placebo, and also the estimation of pain level through the behavioral description and scoring (COMFORT) scale and visual analog scales (VAS) did not differ between the two groups (12).

As a result of the literature review and previous studies, there is a significant difference in the use of non-opioid drugs, especially acetaminophen rather than morphine following abdominal and thoracic surgery in neonates, and the results of studies are inconsistent with each other (13-16). Therefore, in this study, we compared the analgesic effect of acetaminophen with fentanyl that is the conventional analgesic drug used in the NICU in Shahid Motahari and Namazi hospitals in Urmia and Shiraz cities of Iran.

## 2- MATERIALS AND METHODS

### 2-1. Method

This study was conducted as a randomized, double-blind clinical trial in the NICU of two hospitals (Shiraz and Urmia cities, Iran). Considering the shortage in the number of hospitalized patients needed for the sample group, half of the patients (33 patients) were included from the NICU of Namazi hospital in Shiraz and the other half (33 patients) were from the NICU of Shahid Motahari hospital in Urmia, patients were undergoing abdominal and thoracic surgeries. To determine the sample size using the parameters of the study of Espahbadi et al. (10), and 95% confidence interval ($Z_{1-\alpha/2}$:1.96), and power of 95% ($Z_{1-\beta}$: 1.28), the sample size was obtained 33 patients according to the formula for comparing the two means as following:

$$n = \frac{\left(Z_{1-\beta} + Z_{1-\alpha/2}\right)^2}{\left(difference / scale\right)^2}$$

Considering the number of control subjects, 66 patients were enrolled in the study. The sampling was done using convenience method. Regarding the similarity of the implementation of the project, patients were esophageal atresia, diaphragmatic hernia, gastroschisis, duodenal atresia, omphalocele and intestinal obstruction. All patients received the same sedative during surgery. Neonates with a gestational age of 36 weeks and more were included in our study. Also, newborns with a known history of sensitivity to morphine or fentanyl or acetaminophen, newborns with liver dysfunction with elevated alanine aminotransferase (ALT), and aspartate aminotransferase (AST) enzymes levels, newborns with renal dysfunction (such as renal failure, and end stage renal disease) were excluded from the study.

Renal failure was defined as decreased creatinine clearance by 50% and urinary output less than 0.5 ml/kg over a period of 16 h. If the hepatic or renal failure was detected after random sampling, the patient was excluded from the study. After transferring patients to the NICU, for the first control of the pain and ethical issues, a dose of 1 microgram per kg body weight fentanyl was injected to all newborns. The infants were randomly assigned into two groups. One group of patients received fentanyl at a dose of 1 µg / kg (every 6 h), and the other group of neonates received acetaminophen at a dose of 10 mg / kg body weight (every 6 h) intravenously.

For all patients, pain was assessed using the "Neonatal Infant Pain Scale (NIPS)" at first time, 6, 12, 18, 24, 30, 36, 42 and 48 h (9 measurements), which was described in order to familiarize all NICU nursing staff at Shahid Motahar and Namazi hospitals in Urmia and Shiraz with it.. The Neonatal Infant Pain Scale (NIPS) is based solely on behavioral indicators of pain (facial expression, cry, breathing patterns, movements of arms and legs, and state of arousal). The tool uses the behaviors that nurses have described as being indicative of infant pain or distress. It is composed of six indicators, and each behavioral indicator is scored with 0 or 1 (except "cry", which has three possible descriptors and is scored with a 0, 1 or 2). The score ranges from 0 to 7. A score greater than 3 indicates pain. Infants should be observed

for one minute in order to fully assess each indicator (17). The NIPS is easily understood and considered a useful tool for health professionals who work with neonates exposed to painful events. The NIPS was used with internal consistency measured by a Cronbach's alpha of 0.762 (18). The trained nurse did not know the patient grouping. The ward staff did not change during our study. In the case of acetaminophen, if the pain score was greater than or equal to 7; the fentanyl relief dose of 1 microgram per kg body weight was injected in single dose and in the fentanyl group, if the pain score was greater than or equal to 7, fentanyl was injected at a dose of 2 microgram per kg body weight as relief dose. It should be noted that fentanyl relief doses for both groups of patients were repeated up to 3 times, and if the patient needed injection of fentanyl more than 3 times, the patient was removed from the acetaminophen group. In the acetaminophen group, for all patients, the Apotel (Intra venous acetaminophen) was used that has been made in "Exir Iran" company. Also, the fentanyl that was used for the patients was from "Daroo Pakhsh" company of Iran.

### 2-2. Ethics

It should be noted that all parents were informed through a written consent to enter their newborns to the study. No extra charges were imposed on patients. This study was approved by the ethics committee of Urmia University of Medical Sciences prior to its implementation with the code of IR.UMSU.REC.1397.416, and the Iranian Registry of Clinical Trials (IRCT) center with the code of IRCT20171218037936N2.

### 2-3. Statistical analysis

For quantitative variables, the central indicators and dispersion (mean and standard deviation) were calculated and for qualitative variables, frequency and percentage were calculated, and for displaying data, appropriate tables and figures were used. After assessing the distribution of data, in order to be normal, a parametric statistical test such as one-sample t-test and repeated measurement and paired t-test or their non-parametric equivalents were used for comparisons between the two groups. Meanwhile, the significance level of the tests was less than of 0.05 and the data were analyzed through SPSS (version 21.0).

## 3- RESULTS

The aim of this study was to compare the effects of intravenous acetaminophen with fentanyl on 66 neonates including the two groups that underwent thoracic and abdominal surgeries. **Table.1** shows the comparison of quantitative variables measured in the two groups. The mean age of the fentanyl group was 16.79 ± 15.57 days and 16.67 ± 15.77 days in the acetaminophen group. The comparison of mean age of the two groups using t-test showed that there was no difference between the two groups (P = 0.981). The mean weight in the fentanyl group was 3460 ± 737 gr and in the acetaminophen group 3228.548 ± 32.28 gr.

The comparison of the mean weight of the two groups using t-test showed that there was a significant difference between the two groups (P =0.004). The mean gestational age of the fentanyl group was 30.79 ± 14.06 weeks and in the acetaminophen group was 28.12 ± 16.28 weeks, and the mean comparison of the two groups using t-test showed that there was a significant difference between the two groups (P = 0.479). The total duration of surgery in the fentanyl group was 107.28 47 ± 30.4 h and in the acetaminophen group 100 ± 48.23 h and the mean comparison between the two groups showed that there is no significant difference between the two groups (P = 0.539). **Table.2** shows the mean score of pain in the measured times in terms of the

two groups of the study. According to the findings, the mean scores of pain in all periods of time were not significantly different between the two groups using t-test (P> 0.05).

**Table-1**: Comparison of measured quantitative variables between the two groups (n=66).

| Variables | Group | Mean + SD | P-value |
|---|---|---|---|
| Age | Fentanyl | 16.79+15.57 | 0.981 |
| | Acetaminophen | 16.70+15.77 | |
| Weight | Fentanyl | 3460.00+737.10 | 0.042 |
| | Acetaminophen | 3128.48+545.32 | |
| Gestational age | Fentanyl | 30.79+14.06 | 0.479 |
| | Acetaminophen | 28.12+16.28 | |
| Surgery duration | Fentanyl | 107.27+47.30 | 0.539 |
| | Acetaminophen | 100.00+48.23 | |

**Table-2**: Comparison of the Mean of pain scores (NIPS) in the measured periods between the two groups (Fentanyl and Acetaminophen groups).

| Period time | Group | Mean ± SD | P-value |
|---|---|---|---|
| Score at first time | Fentanyl | 3.73±3.15 | 0.299 |
| | Acetaminophen | 2.97±2.72 | |
| Score_6h | Fentanyl | 4.09±2.42 | 0.917 |
| | Acetaminophen | 4.03±2.30 | |
| Score_12h | Fentanyl | 3.24±2.02 | 0.878 |
| | Acetaminophen | 3.15±2.72 | |
| Score_18h | Fentanyl | 2.00±1.66 | 0.710 |
| | Acetaminophen | 2.15±1.64 | |
| Score_24h | Fentanyl | 1.12±1.29 | 0.929 |
| | Acetaminophen | 1.15±1.46 | |
| Score_30h | Fentanyl | 0.79± 0.99 | 0.898 |
| | Acetaminophen | 0.82 ± 0.92 | |
| Score_36h | Fentanyl | 0.52±0.67 | 0.581 |
| | Acetaminophen | 0.42±0.66 | |
| Score_42h | Fentanyl | 0.48±0.67 | 0.225 |
| | Acetaminophen | 0.30± 0.53 | |
| Score_48h | Fentanyl | 0.15± 0.36 | 0.310 |
| | Acetaminophen | 0.27±0.57 | |

Pain ranges from 0 to 7. SD: standard deviation.

Considering that we had 9 measurements of the pain scores during different times in newborns, and to evaluate the mean changes in pain scores over time, and to determine whether these changes were significant between the two groups, the repeat measurement test was used. The results of this test showed that (due to the lack of sphericity of the variance-covariance matrix evaluated by Sphericity test, and the use of Greenhouse-Geisser correction) there was significant difference in the pain scores (P <0.001), but these changes were not affected by the group (there was no significant difference between the two groups) (P = 0.745). Also, the results of the analyses indicate that the pattern of changes in pain scores over time is greater than the linear one, as well as the second-order (Cubic) parabolic model, which was in the form of U, as shown in **Figure.1**.

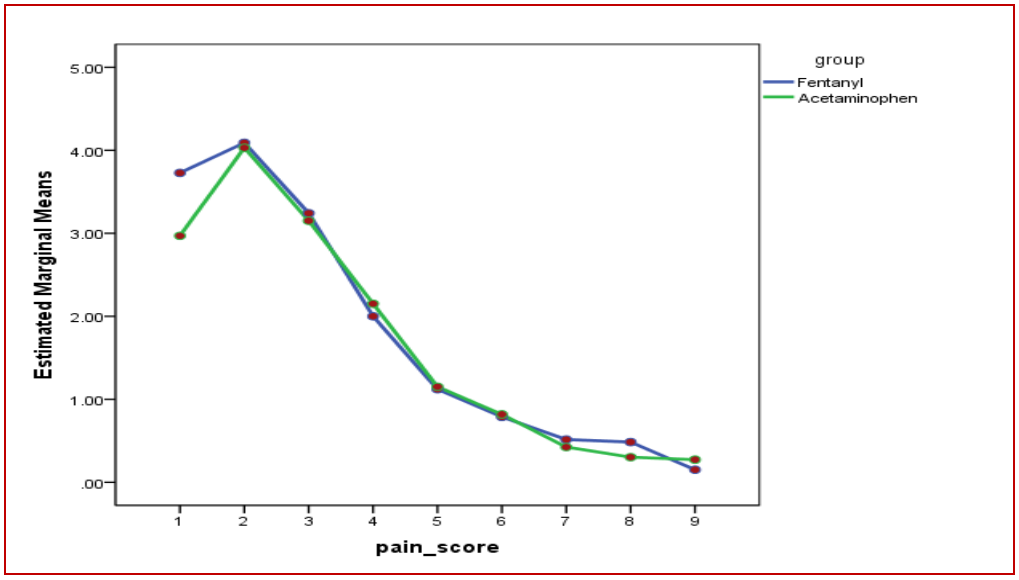


**Fig.1**: Comparison of the mean changes in the pain scores over time between the two groups (Fentanyl and Acetaminophen groups).

**Table.3** shows the mean concentration of fentanyl administered in two groups, based on the mean fentanyl prescribed for fentanyl group (µg/Kg) was 1.91 ± 2.93 and for the acetaminophen group (µg/Kg) it was 1.41 ± 1.71, and there was no significant difference between the two groups using t-test (P = 0.398).

**Table.4** shows the average duration of intubation in two groups, based on the mean duration of intubation time resulted in the fentanyl group 7.28 ± 14.48 h and for the acetaminophen group 6.6 ± 10.34 h. Comparison between the two groups using t-test showed that there was no significant difference (P = 0.733). Based on the results, only in 8 cases of fentanyl group were complications observed, including 4 cases of apnea, 3 cases of urinary retention and 1 case of nausea.

**Table-3**: Comparison of the mean concentration of fentanyl.

| Variable | Group | Mean ± SD | P-value |
|---|---|---|---|
| Fentanyl concentration | Fentanyl | 1.91± 2.93 | 0.398 |
| | Acetaminophen | 1.71± 1.71 | |

**Table 4**: Comparison of the mean duration of intubation time between the two groups.

| Variable | Group | Mean ± SD | P-value |
|---|---|---|---|
| Duration of intubation time | Fentanyl | 7.82± 14.48 | 0.733 |
| | Acetaminophen | 6.76± 10.34 | |

## 4- DISCUSSION

Controlling pain in newborn is very important. As recent studies point out, adequate post-operative pain control can reduce the mortality rate in this population group (2). Ignoring the pain control in newborn can lead to negative consequences on his or her behavior. Evidence suggests that pain and stress in newborn, affects neurological development and later affects perception of painful stimuli and behavioral responses, so pain control can play an important role in the neonatal health and development (17). Various drug categories are used to relieve pain in newborns, including opioid

analgesics, local analgesics, sedative and NSAIDs (2, 4). The results of current study showed that there was no significant difference between the two groups in terms of demographic and general variables such as age, sex, duration of operation and gestational age, and their confounding effect on the parameters under investigation was not significant. Therefore, the results are likely to be related to the effects of drug interventions. According to our study results, fentanyl concentrations used for each patient were 1.91 ± 2.93 μg/kg body weight for fentanyl group and 1.41±1.71 μg/kg body weight for acetaminophen group. There was no significant difference between the two groups using t-test (P=0.398). Therefore, the use of intravenous acetaminophen does not reduce the need for fentanyl.

In both groups, the pain scores decreased similarly with each other over time, and in terms of the mean scores of pain in measured times in both groups, there was no significant difference between the two groups considering that, for ethical reasons we used relief dose of fentanyl in acetaminophen group, when acetaminophen was not able to control pain sufficiently. Concerning the analgesic effect of acetaminophen in surgeries, the results of studies have been controversial. In a study by Heshmati et al. (1), that compared the effect of rectal acetaminophen with pethidine in reducing postoperative pain in children, the pain scores were not significantly different in both groups at measured times. Hence, the results of Heshmati et al.'s study are consistent with this study. In a study by Espahbodi et al. (10) comparing the effects of intravenous acetaminophen and morphine after laparoscopic appendectomy, it was shown that the severity of pain during both recovery and withdrawal from recovery in the morphine recipient group was significantly less than that of the acetaminophen group, which is inconsistent with our study. It should be noted that this study examined the severity of pain in newborns only during the duration of the patient's stay in the recovery, but in our study, the severity of pain measured in patients admitted to the NICU and the measurement of pain periodically was done up to 48 h after surgery. This large difference in follow-up time may affect the outcome of the study. Ceelie et al. (11), also found that paracetamol (acetaminophen) and morphine were effective against pain in children under the age of one year, they showed that, there was a significant difference between the two groups in terms of the mean scores of pain. This shows that results are consistent with our study. In the studies by Joshi et al. (18), and Owen et al. (19), it is also noted that injectable acetaminophen has an equivalent effect of NSAIDs on reducing pain resulting from surgery, which is inconsistent with our study outcomes. In the present study, pain scores were recorded at consecutive times (9 time periods). The results showed that the pain increased up to 12 h, and the downward trend was observed in both groups, which shows a significant difference. Of course, this finding shows that peak pain is up to 12 h after surgery, and afterwards, the pain intensity decreases, which is more important for nursing care during the first 12 h after the operation, which necessitates more attention. In a study by Van Der Marel et al. (12), it has also been shown that acetaminophen does not reduce the need for morphine in major neonatal surgeries. In the study of Heshmati et al. (1), as with our study, the mean of pethidine used after surgery in the two groups did not have a significant difference. However, Korepla et al. (20) noted that the use of rectal acetaminophen reduces the need for morphine to be used for postoperative analgesia. In our study, the mean duration of intubation and mechanical ventilation in the acetaminophen group was 6.76 ± 10.34

and in the fentanyl group was 7.82 ± 14.48, but this difference was not statistically significant. In the study of Ceeli et al. (11), the mean duration of intubation and mechanical ventilation in the morphine recipient group was lower than that of paracetamol, but this difference was not statistically significant. In the present study, 8 cases of complications including 4 cases of apnea (12%), 3 cases of urinary retention (0.09%) and one case of nausea (0.03%) were observed in all of the patients receiving fentanyl and acetaminophen group did not show any of these complications, which suggest that acetaminophen, can better prevent complications. In the study of Heshmati et al. (1), the rate of nausea and vomiting in stage 1 recovery was one case in the pethidine group, and in the 2-h postoperative period, 3 in the pethidine group and in the 4th h post operation, 13 in the pethidine group and 5 in the acetaminophen group, which showed a statistically significant difference. In the study of Espahbodi et al. (10), there was a reduction in complications such as nausea and vomiting in the acetaminophen group. In the study of Ceelie et al. (11), no significant difference was observed in terms of complications in the two groups. In the study of Korpela et al. (20), prescription of rectal acetaminophen reduced postoperative nausea.

### 4-1. Study Limitations

Regarding the parents' sensitivity and concern about their baby, some parents initially refused to participate in the study. For this purpose, detailed and reliable explanations were given to the parents and the parents did not impose on participation in the study. The other limitation of this study was that due to financial constraints, measuring blood levels of the drugs was not possible. Another limitation of this study was the number of samples, that is why the study was designed and implemented as an interventional study and the participation of more infants admitted to the ICU was not easily possible in terms of ethics.

## 5- CONCLUSION

Administration of intravenous acetaminophen intermittently at six-hour intervals in newborn following abdominal and thoracic surgeries does not reduce the need for fentanyl injection. Indicating that, intravenous acetaminophen cannot control pain sufficiently after thoracic and abdominal surgeries in newborns. However, this study showed that acetaminophen administration rather than fentanyl is associated with a reduction in the incidence of complications. It is suggested that more extensive studies should be done to compare the analgesic effects of acetaminophen with fentanyl after neonatal abdominal and thoracic surgeries.

## 6- CONFLICT OF INTEREST: None.

## 7- REFERENCES

1. Heshmati F, Nouroozinia H, Mahoori AR, Mitra Gorji Rad MD. The effect of rectal acetaminophen on post-operative pain control. J Iranian Soc Anaesth Int Care. 2009; 63(64):6.

2. Krishnan L. Pain relief in neonates. Journal of neonatal surgery. 2013; 2(2):19.

3. American Academy of Pediatrics, Fetus and Newborn Committee. Prevention and management of pain in the neonate: an update. Pediatrics. 2006; 118(5):2231-41.

4. Schug SA, Sidebotham DA, McGuinnety M, Thomas J, Fox L. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. Anesthesia & Analgesia. 1998; 87(2):368-72.

5. Simons S. Morphine more fine? Its effects in critically ill newborns. 2004 Mar 18. Available at: file:///C:/Users/saeidim911/Downloads/04031

8_Simons,%20Sinno%20Henricus%20Paulus.pdf.

6. Hall RW, Shbarou RM. Drugs of Choice for Sedation and Analgesia in the NICU. Clinics in perinatology. 2009; 36(1):15-26.

7. Levene M. Morphine sedation in ventilated newborns: who are we treating? Pediatrics. 2005; 116(2):492-3.

8. Haidon JL, Cunliffe M. Analgesia for neonates. Continuing Education in Anaesthesia, Critical Care & Pain. 2010 May 20;10(4):123-7.

9. Pacifici GM, Allegaert K. Clinical pharmacology of paracetamol in neonates: a review. Current Therapeutic Research. 2015; 77: 24-30.

10. Espahbodi E, Ebrahimsoltani A, Molaverdi EZ. Comparing the effect of Acetaminophen with Morphine on decreasing post opearative pain in 3-8 year old children undergoing laparoscopic apandectomy in bahrami hospital. J of Anaesthesiol and Pain .2017. 8 (1): 35-43.

11. Ceelie I, De Wildt SN, Van Dijk M, van den Berg MM, Van Den Bosch GE, Duivenvoorden HJ, De Leeuw TG, Mathôt R, Knibbe CA, Tibboel D. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. Jama. 2013; 309(2):149-54.

12. Van der Marel CD, Peters JW, Bouwmeester NJ, Jacqz-Aigrain E, Van den Anker JN, Tibboel D. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. British journal of anaesthesia. 2007; 98(3):372-9.

13. Hong JY, Kim WO, Koo BN, Cho JS, Suk EH, Kil HK. Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2010; 113(3):672-7.

14. Olischar M, Palmer GM, Orsini F, Davidson AJ, Perkins EJ, Lee KJ, Everest NJ, Cranswick NE, Hunt RW. The addition of tramadol to the standard of IV acetaminophen and morphine infusion for postoperative analgesia in neonates offers no clinical benefit: a randomized placebo-controlled trial. Pediatric Anesthesia. 2014; 24(11):1149-57.

15. Aguirre EC, Durán MG, Zambudio GA, González RC, Castaño IC, Cárceles MB, Gutiérrez MC, Ruiz JJ. Post-surgical paediatric pain: Nursing-PCA vs continuous IV infusion of tramadol. Cirugia pediatrica: organo oficial de la Sociedad Espanola de Cirugia Pediatrica. 2003; 16(1):30-3.

16. Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAID s) in children. Pediatric Anesthesia. 2013; 23(6):475-95.

17. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain.Neonatal Network. 1993; 12(6):59–66.

18. da Motta GD, Schardosim JM, da Cunha ML. Neonatal infant pain scale: cross-cultural adaptation and validation in Brazil. Journal of pain and symptom management. 2015; 50(3):394-401.

18. Anne R. Hansen, Eric C. Eichenwald, Ann R. Stark, Camilia R. Martin. Cloherty and Stark's Manual of Neonatal Care. Preventing and Treating Pain and Stress among Infants in the Newborn Intensive Care Unit. 8th Ed. Philadelphia: Wolters Kluwer Health, 2016; pp.1022-41.

19. Joshi G, Bonnet F, Kehlet H. Evidence-based postoperative pain management after laparoscopic colorectal surgery. J Colorectal Disease.2013; 15(2):146-55.

20. Owen H, Plummer JL, Ilsley AH, Tordoff K, Toouli J. Pain control in the week following laparoscopic surgery: a comparison of sustained-release ibuprofen and paracetamol. J Minimally Invasive Therapy Allied Technologies 1997; 6(3): 235-40.

21. Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. The Journal of the American Society of Anesthesiologists. 1999; 91(2):442-7.