Intravenous Bolus Fentanyl vs. Rectal Acetaminophen in Outcome and Quality of Anesthesia in Infants Undergoing Pyloromyotomy: A Randomized Clinical Trial

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Abstract

Background

Hypertrophic Pyloric Stenosis (HPS) is one of the most common diseases requiring surgery in infants. Regardless of recruited surgical reconstruction techniques, preoperative evaluation, using proper anesthesia induction, perioperative, and postoperative care are the main determining factors in the outcome of these patients. This study aimed to evaluate and compare the premedication with intravenous fentanyl versus rectal acetaminophen on the anesthesia-related outcome of patients.

Methods

In this double-blinded randomized clinical trial, 24 infants who were managed to underwent a pyloromyotomy surgery due to the HPS were enrolled. Patients then randomly allocated into two groups of Fentanyl (F) or Acetaminophen (A). Anesthesia procedure was initiated with premedication with midazolam (0.03 mg/kg) co-administrated with fentanyl (1 µg/kg) in group F, and rectal acetaminophen (40 mg/kg) administrated 20 minutes prior to midazolam (0.03 mg/kg) in group A individuals. All patients' vital signs, the period of each step of anesthesia, and the incidence of apnea were measured and recorded.

Results

Although the time duration from anesthesia termination till extubation and the recovery time were relatively shorter among the patients of the acetaminophen group, there were no statistically significant differences between the two groups. Patients in the acetaminophen group showed a lower level of pain in all evaluated timelines than those who were treated with fentanyl ($p < 0.05$). There was no statistically significant difference between the apnea incidence in two groups.

Conclusion

The use of rectal acetaminophen in infants who are planning to undergo pyloromyotomy due to HPS offers a better treatment outcome than fentanyl.

Trial Registration:

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the registry code of IR.TBZMED.REC.1397.511. It was also registered in Iranian Registry of Clinical Trials (IRCT). The trial's registration number (TRN) is IRCT20180726040601N1 **'retrospectively registered'**

Background

Hypertrophic Pyloric Stenosis (HPS) is one of the most common diseases requiring surgery in infants. The disease is widespread worldwide and is particularly common in Caucasians descent. Its incidence is 0.9-1.5 per 1000 live births and is generally diagnosed in early infancy [1-4].

The definitive treatment for HPS is performing surgical pyloromyotomy in order to eliminate the obstruction. What is important here is not only the surgical procedure but correcting and meticulously monitoring the patients' electrolyte imbalances and dehydration, which is caused by profound and consecutive vomiting. Hence, regardless of laparoscopic or laparotomic reconstruction, preoperative evaluation, using proper anesthesia induction, perioperative, and postoperative care are the main determining factors in the outcome of these patients [2, 5, 6].

Also, it should be noted that poor control of pain in infants can lead to subsequent hyperalgesia and chronic pain. Ketamine and acetaminophen are the suggested alternative postoperative analgesic medications. Some studies revealed that the use of ketamine links to an increase in the risk of laryngospasm. Meanwhile, acetaminophen usually procures the primary analgesia during and after surgery; also, it does not have the postoperative respiratory complications of opioids. Therefore, acetaminophen could be considered as a wise choice in this setting [4, 6-8].

Now all the data mentioned above pop-up these questions:

1. Since the pyloromyotomy is a relatively minor operation in which there is limited surgical stress imposes to the patient, is there a necessity for using opioids during this surgery? In other words, is acetaminophen as effective as opioids in order to reach the optimal analgesic goals?
2. If the answer to the above question is negative, and we were forced to use opioids during surgery, will the patients' emergence and recovery phases sustain for a long time? Will it associate with an increased incidence of postoperative apnea? (according to the fact that acetaminophen does not have such effects on the infants)
3. If the answer to the first question is yes, do these patients also experience prolonged recovery time and apnea occurrence even without using opioids? (if this scenario happens, we should look for causes other than opioids)

So, we designed and conducted this study, intending to answer these important questions which are directly related to the prognosis and outcome of children who suffer from HPS.

Methods

Patients recruitment

In this double-blinded randomized clinical trial, 24 infants who were managed to underwent a pyloromyotomy surgery due to the HPS in Children hospital of Tabriz University of Medical Science were

enrolled. Patients then randomly allocated into two groups of Fentanyl (F) or Acetaminophen (A) via simple random allocation method. Regarding our randomization protocol patients' guardians, surgeon, the physician who were in charge for postop evaluation of patients and all nurses and care providers who were somehow involved in patients' care keep blinded. All patients -regardless of which study group they were in- were summoned and gathered into the pre-op preparation room 20 minutes prior to the surgery in order to keep the parents blinded. Only the anesthesiologist who were responsible for the whole anesthesia procedure was aware of the groups.

According to the previous study by Khalifa et al., a minimum sample size of ten individuals was calculated for each group (95% test power, 5% first-degree error). By adding 20% to this value as a probable drop-off a number of 12 individuals have been recruited for each F and A group.

Children older than two months, bodyweight less than 2.5 kg, preterm infants, serum hemoglobin level less than 10 mg/dl, venous blood HCO_3^- more than 30 mmol/L, venous blood pH more than 7.55 were considered as the exclusion criteria. It also indicated that if the use of an opioid or a muscle relaxant agent was inevitable during the surgery, these medications are allowed to be used under the decision of the surgeon or anesthesiologist but, that particular patient should be excluded from the study.

Study Protocol

According to inclusion and exclusion criteria, 24 children with a diagnosis of hypertrophic pyloric stenosis who were candidates for pyloroplasty were randomly selected and assigned into one of fentanyl (F) or acetaminophen (A) groups. Samples for CBC and VBG obtained, and blood gas profile was corrected. After proper preoxygenation, anesthesia procedure was initiated with premedication with midazolam (0.03 mg/kg) co-administrated with fentanyl (1 µg/kg) in group F, and rectal acetaminophen (40 mg/kg) administrated 20 minutes prior to midazolam (0.03 mg/kg) in group A individuals. Subsequent to this point, the whole procedure was the same for both groups; following premedication, gastric decompression was performed by the placement of a 10fr nasogastric (NG) tube. After evacuating the gastric contents in supine, left, and right lateral decubitus positions, the NG tube was discharged. At this point, Lidocaine (1 mg/kg) and atropine (0.02 mg/kg) were injected intravenously, and one minute later, awake intubation was performed. After making sure that the endotracheal tube was placed in the proper position by the aid of auscultation and capnography, propofol was administered intravenously with a dose of 3 mg/kg. Sevoflurane 2.5% mixed with 50% pure oxygen and 50% air mixture with the flow of 4 L/min commenced afterward as the maintenance of anesthesia till the end of the surgery.

All patients' heart rate (HR), functional oxygen saturation (SpO_2) systolic, and diastolic blood pressure were measured regularly during anesthesia and recorded in the specific timetable. The duration of anesthesia (time interval from midazolam administration until cutting off sevoflurane) was also recorded. In both groups, anesthetic agents were discontinued as soon as surgery terminated. Fully awake extubation was performed, and the time interval between anesthetic agents discontinuation and extubation was recorded. According to the modified Aldrete scoring system [9], the recovery period, as well as, number of apnea episodes that occurred during the recovery phase, were recorded.

Postsurgical pain assessment carried out using the FLACC score [10], which is a nonverbal behavioral pain estimating scale for pediatrics (Table-1). In the case of FLACC > 4, PO or rectal acetaminophen was given with a dose of 15 mg/kg Q6H. The demand for acetaminophen in order to postoperative pain management was recorded in both groups. Post extubation pain score was recorded in all patients at the time of extubation and one hour later in the recovery section. Also, this score was recorded in the pediatrics surgery ward as soon as the patient arrived at the ward, then 2, and 4 hours later. All infants were monitored for apnea during their stay in the surgery ward. In the case of apnea, the number of spells was recorded.

Statistical Analysis

All Data were analyzed by SPSS version 23.0. (IBM Corp., Armonk, N.Y., USA) and reported by frequency and percentage for qualitative variables and with mean and standard deviation in quantitative variables. Stratification was used to eliminate confounding effects. Independent sample/ student t-Test and ANOVA were used for analyzing continuous variables. Discrete variables were compared by the chi^2 and fisher exact test. The p-value ≤ 0.05 was considered as statistically significant.

Ethical Consideration

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the registry code of IR.TBZMED.REC.1397.511. It was also registered in Iranian Registry of Clinical Trials (IRCT) with the registration reference of IRCT20180726040601N1.

No additional intervention or cost was imposed on patients in this study. Patients' data were entered into the study as an encoded parameter anonymously. The personal information of none of the patients was included in this research, and only their statistical analysis was presented in general. The written informed consent was obtained from the parents or legal custodians of each participant. The patients whom their parents or legal custodians did not sign the informed consent form were excluded from the study.

Results

Twenty-four infants aged between 10 days to two months were enrolled in this study. There was no difference in the patient's age, gender, and weight between the two groups. Table-2 compares the demographic information between the two study groups. The final lab results of the patients (consisting of blood gas analysis, hemoglobin, and hematocrit) are also shown in Table-2, stratified by the groups.

The values of anesthesia duration (T1), the time duration from anesthesia termination till extubation (T2), and the recovery time (T3) were compared between two groups. As shown in table-3, there was no statistically significant difference between the two groups in the above mentioned periods. But, as demonstrated in figure-1, the T2 and T3 times were relatively shorter among the patients of the acetaminophen group, which was clinically significant.

In determining the postoperative pain in patients via FLACC score, the differences between the two groups were statistically significant, and patients in the acetaminophen group showed a lower level of pain in all evaluated timelines than those who were treated with fentanyl (Table-4, Figure-2). The apnea was reported among two patients in group F, and one patient in group A, one episode in each patient. The difference was not statistically significant ($p = 0.537$).

There was no statistically significant difference between the two groups in the amount of acetaminophen used during recovery and in the first, second, and fourth hours after the patient's been discharged from recovery ($p > 0.05$).

Discussion

In the setting of hypertrophic pyloric stenosis in order to reach optimal patient care and better prognosis, various induction, maintenance, and postop recovery care have been developed. One of the major concerns among these patients' anesthesia is to decrease the duration of emergence and recovery steps. Prolongation of these steps may increase the risk of apnea among the patients. On the one hand, prolongation of the recovery phase is related to alkalemia and concomitant increase in cerebrospinal fluid pH, which is believed to be the culprit for the occurrence of apnea. On the other hand, using opioids for analgesia also has been implicated in prolongation of the recovery phase [11–14].

As discussed in section-1, choosing the proper anesthesia method is way more important and rather challenging than surgery technic among the patients with hypertrophic pyloric stenosis. Furthermore, current literature brings more questions in mind than answers regarding the use of proper analgesic methods during anesthesia induction in these patients. However, this clinical trial provides remarkable information responding to some of these questions.

Based on the literature, HPS generally expected to occur in the first offspring of the family and mostly among male infants [15]. In this study, likewise, the literature number of affected males was more than females (M: F = 3:1).

During the recovery, infants should be monitored for apnea, respiratory failure, and drop in body temperature related to metabolic alkalosis [16]. There were no cases of postoperative apnea or alteration in blood gas status found among our studied patients.

Based on a study by Galinkin J.L. et al., premature infants are more commonly prone to experience apnea following pyloroplasty surgery. However, it does not mean term infants are protected against apnea, and it may happen among all children undergoing pyloroplasty surgery regardless of their gestational age [17]. In our study, all patients had controlled respiratory pattern and did not develop apnea.

In the present study, the total anesthesia duration time (T1), the time duration from anesthesia initiation till extubation (T2), and the recovery time (T3) were recorded and compared between two groups. According to obtained data, although the differences in those variables are not significant between two

groups, the patients in the acetaminophen group showed clinically significant lower duration in time required for extubation and the time spent in recovery. This clinical discrepancy is not dismissible, and the statistical results may have occurred due to the smallness of the sample size.

In a study by Yung A. et al. comparing the analgesic effects of intravenous versus rectal acetaminophen on 68 patients who underwent a pyloroplasty surgery owing to HPS, the authors revealed that there was no difference in pain control in intravenous and rectal acetaminophen. Hence, they suggested that the use of the rectal form of acetaminophen could be substituted with the conventional IV route among these children [4].

In this study, patients of the two groups were compared in the context of postoperative pain using the FLACC score, which showed lower pain experience among the patients who were treated with rectal acetaminophen, though the pattern showed a downtrend pain rate in both groups. We believe that this has happened because of the shorter half-life of fentanyl compared to acetaminophen. As demonstrated in figure-2, spending an hour after surgery, the analgesic effect of fentanyl was diminished, and it results in an increase in mean FLACC score among group F patients. Adding this to the other advantages of the acetaminophen compared to fentanyl -which is safe, has fewer side effects, well tolerable without CNS depressant effects- makes rectal acetaminophen a better choice than fentanyl for analgesic purposes among these patients. Moreover, the rectal route of administration of acetaminophen does not have disadvantages of the intravenous route [4, 18–20].

Alongside the strength of the current study toward answering the ambiguity in previous researches, it also has some limitations. The shortness of the study sample size was the most important of them. Moreover, the method of evaluating apnea among the patients was the other limitation of this study. The recent limitation emerged from the shortage of equipment in the center in which the study was conducted.

Conclusion

In sum, according to the results of this study, it can be concluded that the use of rectal acetaminophen in infants who are planning to undergo pyloromyotomy due to HPS offers a better treatment outcome than fentanyl.

Abbreviations

HPS
Hypertrophic Pyloric Stenosis
CBC
Complete Blood Count
VBG
Venous Blood Gas
NGT

Nasogastric Tube
FLACC
Face, Leg, Activity, Cry, Consolability (a pain measurement scale for children)
IRCT
Iranian Registry of Clinical Trials (a Primary Registry in the WHO Registry Network)

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the registry code of IR.TBZMED.REC.1397.511. It was also registered in Iranian Registry of Clinical Trials (IRCT) with the registration reference of IRCT20180726040601N1.

No additional intervention or cost was imposed on patients in this study. Patients' data were entered into the study as an encoded parameter anonymously. The personal information of none of the patients was included in this research, and only their statistical analysis was presented in general. The written informed consent was obtained from the parents or legal custodians of each participant. The patients whom their parents or legal custodians did not sign the informed consent form were excluded from the study.

Consent for Publication

Written informed consent was obtained from the patients' parents or their legal guardians alongside with the trial participation consent.

Availability of Data and Materials

- The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

- The authors declare that they have no competing interests

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- Not applicable. No financial support is required for the current study

Authors' contributions

- B.A.S., D.S., and M.S.H. conceived of the presented idea B.A.S., D.S. selected the patients. B.A.S., D.S. and N.A. provided the management methods with the supervision of M.S.H, S.P. N.A. and S.A. contributed to follow-up data acquisition. S.P. and S.A. acquired additional data from the database.

S.P. analyzed the data. S.A. and S.P. wrote the manuscript. B.A.S and D.S. revised the manuscript. M.S.H. supervised the whole project.

All authors have read and approved the final manuscript.

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- Not applicable

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Tables

Table-1: FLACC scoring system

	Score		
Categories	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Leg	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complains
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Table-2: demographic status and lab results of study participants

Value		Group A		Group F		p-value
Mean Age (days)		35.7 ± 19.1		36.5 ± 18.9		0.91
Sex		Boy	Girl	Boy	Girl	0.356
		8 (66.7%)	4 (33.3%)	10 (83.3%)	2 (16.7%)	
Mean Body Weight (g)		3600 ± 923.4		3775 ± 537.8		0.576
Lab Results						
VBG	pH	7.43 ± 0.04		7.44 ± 0.04		0.349
	HCO_3^-	26.6 ± 4.96		28.9 ± 5.07		0.293
	CO_2	41.5 ± 7.3		42.9 ± 6.99		0.638
	BE	2.51 ± 4.43		4.4 ± 4.28		0.293
CBC	Hb	12.3 ± 2.35		13.1 ± 1.14		0.301
	Hct	36.2 ± 5.73		38.7 ± 4.1		0.230

(VBG: Venous Blood Gas, CBC: Complete Blood Count, HCO_3^-: Bicarbonate, CO_2: Carbone dioxide, BE: Base Excess, Hb: Hemoglobin, Hct: Hematocrit)

Table-3: comparison of important time periods between study groups.

	Group A	Group F	p-value
T1 (minutes)	25.7 ± 6.6	23.75 ± 8.4	0.527
T2 (minutes)	56 ± 21.2	63.3 ± 22.5	0.451
T3 (minutes)	38.8 ± 15.8	52.2 ± 18.7	0.072

(T1: anesthesia duration, T2: time duration from anesthesia termination till extubation, T3: recovery duration)

Table-4: mean FLACC score of each group

FLACC Score	Group A	Group F	P-value
Discharge from recovery (reference)	1.16 ± 1.8	1.33 ± 2.3	0.846
1 hour later	0.83 ± 1.58	2.5 ± 1.97	0.033
2 hours later	0.58 ± 1.5	2.0 ± 1.7	0.042
4 hours later	0.5 ± 1.44	0.91 ± 0.99	0.420

Figures

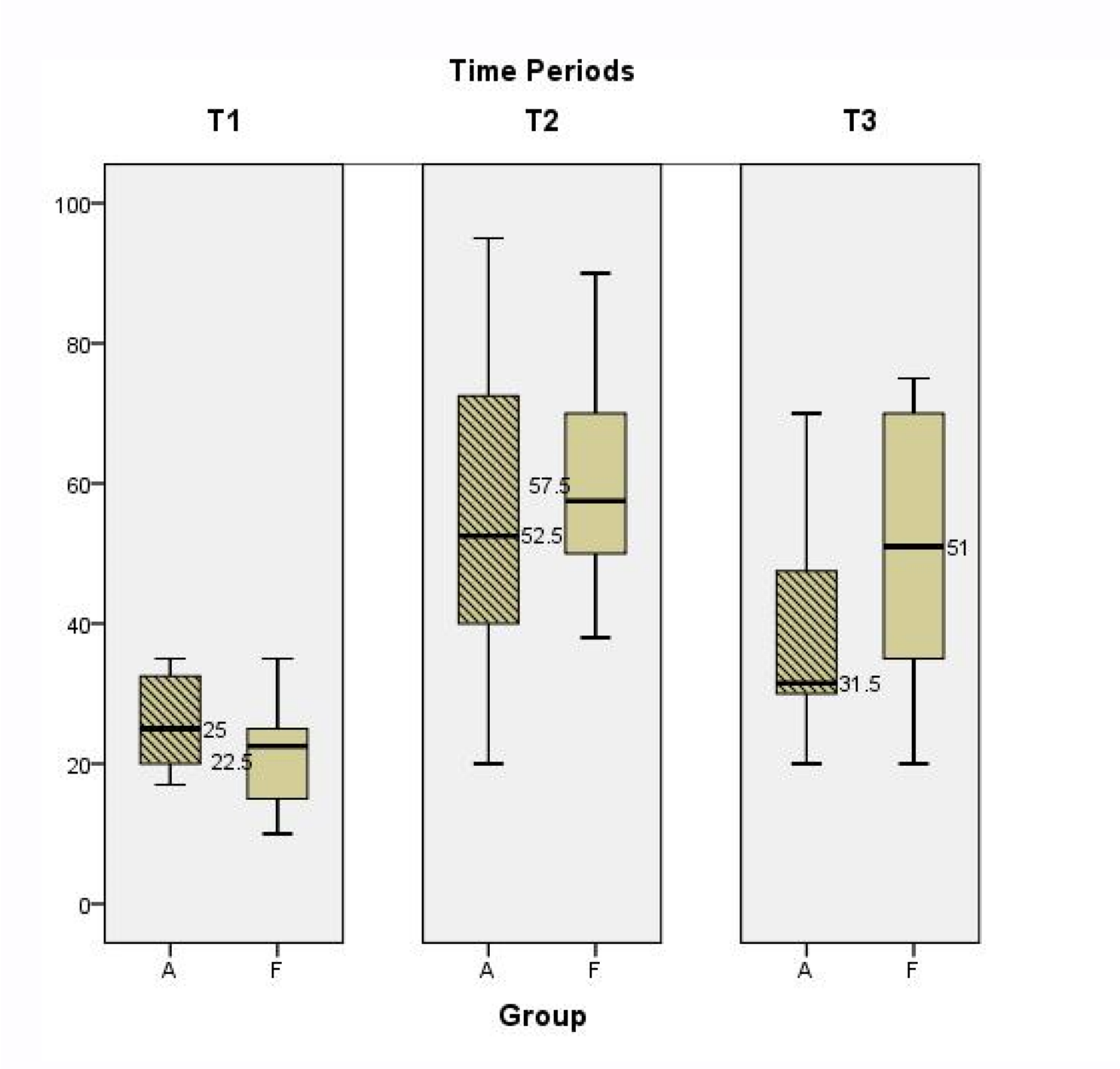

Figure 1

important time intervals in each study group. (T1: anesthesia duration, T2: time duration from anesthesia termination till extubation, T3: recovery duration)

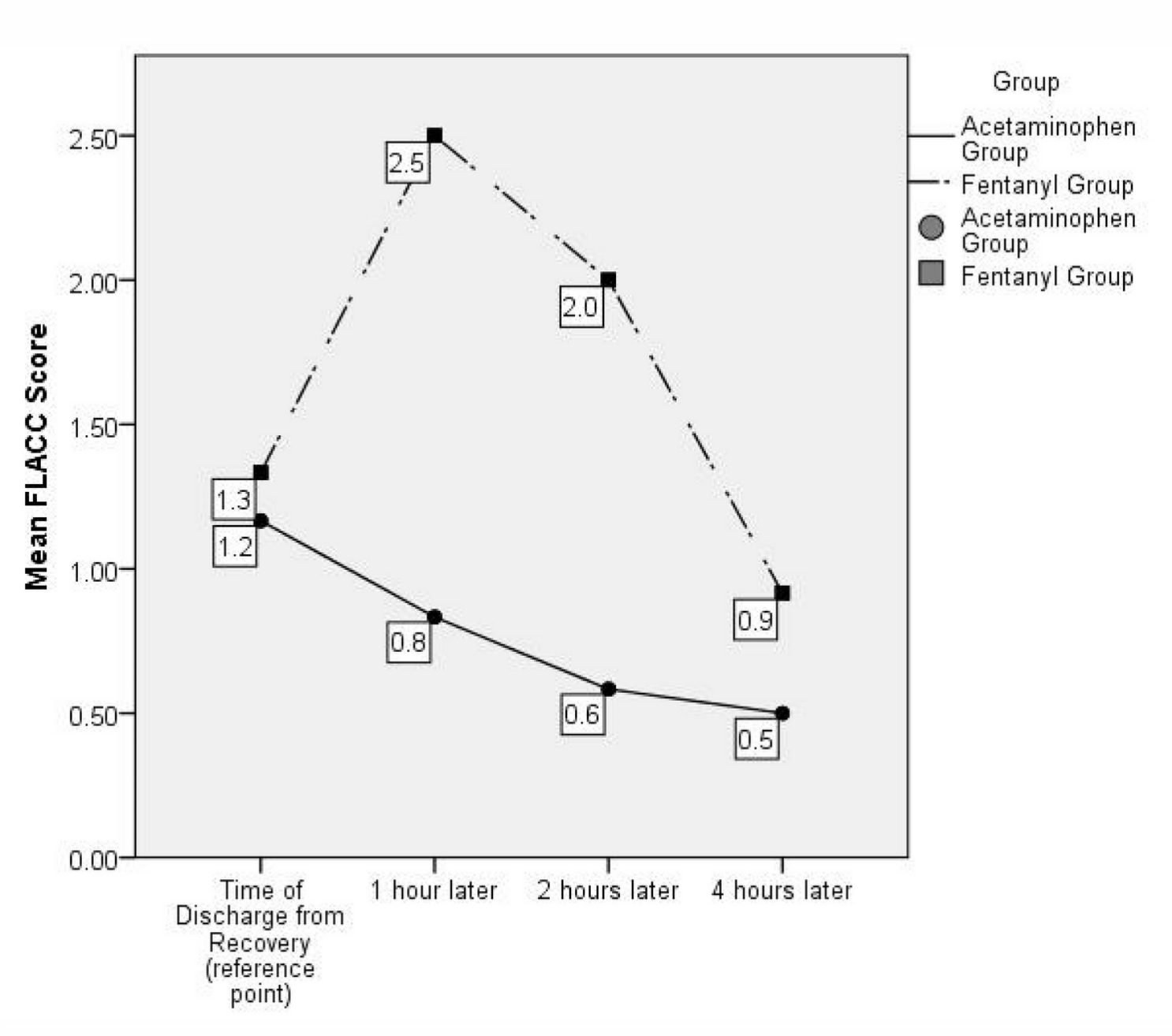

Figure 2

mean FLACC score in each group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTFlowDiagramFentanylvs.Acetaminophen.doc
- CONSORTChecklistFentanylvs.Acetaminophen.doc