

Use of Low Dose Oral Midazolam During Invasive Procedures in Pediatric Hematology Patients

Pediyatrik Hematoloji Olgularında İnvazif Girişimler Öncesinde Düşük Doz Oral Midazolam Kullanımı

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ABSTRACT

Objective: Children with hematological diseases (especially with leukemias) often undergo painful procedures that adds more stress to their underlying illness. The aim of this study was to investigate whether oral midazolam can decrease fear and distress when given together with usual intravenous sedoanalgesia.

Methods: A total of 47 patients with 1- 18 years of age who were followed at hematology inpatient setting were included in the study. The study group consisted of patients undergoing bone marrow aspiration or lumbar puncture for acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), immune thrombocytopenic purpura (ITP), thrombocytosis, chronic myeloid leukemia (CML) and aplastic anemia. Patients were divided into placebo (n=23) and oral midazolam (n=24) groups in this double-blind randomized study. Midazolam group received 0.1 mg/kg (maximum 10 mg) orally 30 minutes before the procedure. Both groups were administered 0.5mg/kg ketamine intravenously before the procedure. Parents and children >7 years reported their fear and distress with visual analogous scale (VAS) and Wong-Baker FACES Scale. CHEOPS score was filled by the blinded pediatric hematologist performing the procedures.

Results: There was no difference of fear and distress levels of placebo and midazolam groups according to VAS, Wong Baker FACES and CHEOPS scores (p>0.05). We found no additional effect in decreasing pain and stress of oral midazolam versus placebo when administered together with intravenous ketamineanalgesia. Nausea according to analgesia was found to be more reduced in the midazolam group (p< 0.05).

Conclusion: Low dose oral midazolam does not have an additional effect in decreasing fear and distress in pediatric hematology patients when administered together with intravenous ketamineanalgesia. More studies to evaluate its effect when used without intravenous analgesia is warranted.

Key Words: Midazolam, invasive procedures, pediatric hematology

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ÖZET

Amaç: Çocukluk çağında hematolojik hastalığı olan olgular sıklıkla kemik iliği aspirasyonu ve lomber ponksiyon ile intratekal kemoterapi verilmesi gibi ağrılı invazif girişimsel işlemlere maruz kalmakta ve bu durum altta yatan hastalığın neden olduğu stresi artırmaktadır. Çalışmamızın amacı intravenöz sedoanaljezi ile beraber kullanılan oral midazolam tedavisinin olguların invazif girişimsel işlem kaynaklı korku ve stres üzerine etkisinin araştırılmasıdır.

Yöntemler: Yaşları 1-18 yaş arasında değişen toplam 47 olgu çalışmaya dahil edildi. Hasta grubu akut lenfoblastik lösemi (ALL), akut myeloblastik lösemi (AML), immün trombositopenik purpura (İTP), trombositoz, kronik myeloid lösemi (KML) ve aplastik anemi tanılılarıyla kemik iliği aspirasyonu veya lomber ponksiyon yapılan olgulardan oluşmaktaydı. Çift kör randomize kurgulanan çalışmamızda, olgular Plasebo grubu (n=23) ve Midazolam grubu (n=24) şeklinde sınıflandırıldı. Midazolam grubuna işlemden 30 dakika önce 0.1 mg/kg (maksimum 10 mg) oral midazolam içeren meyve suyu, Plasebo grubuna ise ilaçsız meyve suyu uygulandı. Her iki gruba işlemden hemen önce 0.5 mg/kg intravenöz ketamin uygulandı. İşlem sonrası 7 yaş altı olguların ebeveynlerine, 7 yaş üstü olguların kendilerine Vizuel Analog Skalası (VAS) ve Wong Baker Yüz Skalası uygulanarak korku ve stres dereceleri ölçüldü. CHEOPS skoru ise girişimleri uygulayan pediyatrik hematoloji uzmanı tarafından değerlendirildi.

Bulgular: Plasebo ve midazolam grubunda VAS, Wong Baker Yüz Skalası ve CHEOPS skorları açısından fark saptanmadı (p>0.05). Plasebo ile karşılaştırıldığında oral midazolamın ağrı, korku ve stresi azaltmada katkısı sağlamadığı saptandı (p>0.05). Midazolam uygulanan grupta bulantı yan etki olarak daha az oranda saptandı (p<0.05).

Sonuç: Pediyatrik hematoloji olgularında yapılan invazif girişimsel işlemlerde intravenöz ketamin ile beraber kullanılan oral midazolamın işleme bağlı korku ve stresi azaltma konusunda etkili olmadığı görüldü. İntraenöz analjezi kullanılmadan oral midazolam etkisinin araştırılması amacıyla daha fazla randomize çalışmaya ihtiyaç olduğu düşünüldü.

Anahtar Sözcükler: Midazolam, invazif girişim, pediyatrik hematoloji

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INTRODUCTION

Children with hematological diseases (especially with leukemia) often undergo painful procedures that add more stress to their underlying illness. These procedures often give rise to considerable fear, pain and distress in children (1-3). It has been shown that children are sometimes under-treated with analgesia during bone marrow aspirations and lumbar punctures (4). Many anesthetic agents and routes of administration including ketamine, fentanyl, intravenous midazolam and topical eutectic mixture of lidocaine and prilocaine (EMLA® cream) have been studied in the management of procedure related pain and distress (5 -7). Oral midazolam has been found to reduce fear and anxiety when compared to placebo in cancer patients undergoing painful procedures (8). The aim of the study was to investigate whether oral midazolam can decrease fear and distress when given together with intravenous ketamine analgesia in pediatric hematology patients.

METHODS

The present double-blind randomized placebo- controlled study was performed at Gazi University Medical School Pediatric Hematology Unit within a six-month period after approval by Institute Ethics Committee of our hospital. Written informed consents were obtained from parents of all children. The exclusion criteria were: children <1 years or >18 years; having pain more than >50 on a 100 mm VAS scale before invasive procedure, nausea, known allergic reaction to EMLA, midazolam or ketamine. A total of 47 patients (between 1 to 18 years of age) followed by pediatric hematology outpatient clinic were eligible for the study. Demographic characteristics and the diagnoses of patients were presented in Table 1.

Procedure and evaluation

The parents and children >5 years were given information about the study and were asked for their consent. Children were randomly assigned to two groups with computer generated random number chart by one of the study investigators (HK) according to two batch series containing either oral midazolam (0.1 mg/kg at a maximum dose of 10 mg) mixed with orange juice or orange juice alone. Children were kept nil orally for 6 hours before the procedure, but only allowed to receive either placebo or midazolam per orally 30 minutes before lumbar puncture or bone marrow aspiration. All children were treated with EMLA® cream to the body region of application at the 60 minutes before the procedure. Investigator performing the procedures (FBB), children and parents were blinded to the treatment allocation until statistical data analysis was completed. During the procedure all children were monitored for continuous electrocardiogram, heart rate and pulse oximetry. Nasal O₂ 2L/min was administered to all children. Both groups received 0.5 mg/kg ketamine intravenously before the procedure. Two hours after the procedure, parents and children >7 years reported their fear, and distress with visual analogous scale (VAS) and Wong-Baker Facies Scale. CHEOPS score was filled by the blinded pediatric hematologist (FBB) performing the procedures (9 -11). After the procedure, all children were observed for 2 hours and followed for side effects like nausea, headache and vomiting.

Statistical Analysis

Statistical analyses were performed with SPSS 11.5 with Windows package programme. Results were expressed as mean and minimum maximum values. The patient numbers in the groups were designated as 'n' and percentages of the patients were expressed as '%'. Data were analyzed for normality with Shapiro-Wilk test. The significance of means between the groups were analyzed with student T-test, while difference of medians were analyzed with Mann Whitney U test. Nominal data were analyzed using Pearson's Chi-square and Fischer Exact test. P value <0.05 was considered as significant.

RESULTS

A total of 47 patients with a median age of 9.8 ± 5.8 (2-18 years) were included in the study where placebo (control) and midazolam (study) groups consisted of 23 and 24 patients, respectively. The diagnoses of children included 12 ALL, 6 AML, 3 ITP, 1 thrombocytosis, 1 CML in placebo group and 15 ALL, 3 AML, 1 ITP, 2 thrombocytosis, 1 CML and 2 AA in the midazolam group. The distribution of the groups according to age, body weight, time from initial diagnosis and time from the last invasive procedure were similar ($p>0.05$) (Table 1).

The procedures included 52.2% (n=12) lumbar punctures and 47.8% (n=11) bone marrow aspirations in placebo group and 45.8% (n=11) lumbar punctures and 54.2% (n=13) bone marrow aspirations in midazolam group. Fear, distress, pain, difficulty in taking the drug was found similar in midazolam and placebo groups according to VAS score ($p>0.05$). There was also no significant difference of scores due to Wong-Baker scale among the two groups ($p>0.05$). According to CHEOPS observations, the placebo and midazolam group both got a mean score of 7 showing no difference among two groups ($p>0.05$) (Table 2). However, procedure time (minutes-from beginning from the needle insertion until full awakening of the patient) was shorter in midazolam group (mean midazolam/placebo=60/65 $p=0.027$). No unexpected serious events were reported. Headache, nausea and tremor were minor side effects reported. None of the children had desaturation during the procedure. The incidence of nausea was less in midazolam group when compared to placebo group ($p=0.018$).

DISCUSSION

Although we hypothesized that oral midazolam would decrease fear and distress among pediatric hematology patients undergoing painful procedures, we could not detect a difference between placebo and midazolam groups in terms of VAS, Wong-Baker Facies and CHEOPS scores. This finding was not consistent with a previous study by Heden et al. who found that low dose oral midazolam decreased fear during needle procedures of children with cancer (8). The observation that the children in that study had much higher mean scores in both midazolam and placebo groups may be attributed to the fact that they did not use intravenous sedation other than oral midazolam as we did in our study. The addition of intravenous ketamine (0.5 mg/kg) in both midazolam and placebo groups could have masked the actual effect of midazolam on fear and distress. Comparing mean values, pain seemed to be a little problem when compared to fear in our study (pain/fear 5/7 and 4.5/7 in placebo and midazolam groups respectively). It has been shown that young children < 6 years may have problems with describing their feelings of fear and pain about a procedure that is why Wong Baker Facies Scale was also added to our assessment (12). As we thought VAS can be appropriate to assess symptoms like fear and distress connected to pain (13), we used it for both parents and children. Fear, distress, pain, difficulty in taking the drug was found similar in midazolam and placebo groups according to VAS score ($p>0.05$). There was also no significant difference in scores due to Wong-Baker scale between the two groups ($p>0.05$). According to CHEOPS observations, the placebo and midazolam group both got a mean score of 7, showing no difference between the two groups ($p>0.05$). However, procedure time (minutes-from beginning from the needle insertion until full awakening of the patient) was shorter in midazolam group (mean midazolam/placebo=60/65 $p=0.027$), which was consistent with a previous report (8). Interestingly, nausea was found to be less in midazolam group as compared to placebo group (3/10 patients respectively, $p=0.018$). In a prospective randomized double blind study by Yadav G et al., it was shown that oral midazolam was effective in control of post operative nausea and vomiting when compared to placebo similar to anti-nausea effect in our study (14).

CONCLUSION

A low dose of oral midazolam does not have an additional effect in decreasing pain and stress in pediatric hematology patients when administered together with intravenous ketamine analgesia. More studies are needed to evaluate its effect when used without intravenous analgesia.

Conflict of Interest

No conflict of interest was declared by the authors.

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