Research Article

Gender Difference in Early Pain After Craniotomy
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Summary

Objective (Background): The aim of this study was to determine the aetiology, quality and quantity of the pain following craniotomy during early postoperative period with using visual analogue score (VAS) and verbal rating scale (VRS).

Methods: All craniotomy patients received 5 mg kg⁻¹ Thiopental, 2 mcg kg⁻¹ Fentanyl, 0,6 mg kg⁻¹ rocuronium for induction of anesthesia, and 0,1- 2 mg kg hrs⁻¹ propofol, 0,15-1,00 mcg. Kg⁻¹ min⁻¹ remifentanil infusions with 50% oxygen-air mixture and additional doses of rocuronium (0,15 mg kg⁻¹) for maintenance of anesthesia. Before craniotomy, scalp around incisional area was infiltrated with 20 ml local anesthetic (1% lidocaine with 35 mcg. mL⁻¹ adrenaline). All patients' age, weight, height, gender and location of surgical incision (supratentorial or infratentorial), the cause (vascular or tumor) and the duration of the surgery was recorded. All patients' heart rate, systolic and diastolic blood pressure, Ramsay sedation status scale was assessed and reported at 0., 30th. and 60th. minutes after operation and during discharge time from post anesthesia care unit (PACU). Patients who were unconscious before or after surgery, with limited cooperation and impaired cognitive functions were excluded from the study.

Results: In the early post-operative period, following craniotomy, the pain was mild to moderate according to VRS, and the pain was disturbing according to VAS scores of the patients. The average scores were 3.91± 2, 45 for VAS and 1.40 ± 1,08 for VRS at 0. minute of postoperative period. There was statistically significant decrease in VAS and VRS scores at 30. and 60. minutes. In women at 0. min and 1. hours VAS- VRS scores were higher than in men's VAS- VRS scores (p<0,05).

Conclusions: We found that, there is mild to moderate pain following craniotomy. We conclude that, it is probably due to local anesthetic infiltration of surgical scalp area before surgical incision. We couldn't find any correlation or statistically significant relationship according to VAS and VRS with supratentorial or infratentorial surgical approaches, different surgical incisional style, vascular or tumoral pathology, ASA status of the patients, age range and duration of surgery. There was significant correlation only with gender and the early pain following craniotomy.

Key words: Craniotomy, postoperative pain, gender effect

Kraniyotomi Sonrası Erken Ağrıda Cinsiyet Farkı

Özet

Amaç: Bu çalışmanın amacı postoperatif erken dönemdeki postoperatif ağrının etiyolojisini, niceliğini ve niteliğini vizüel analog skala (VAS) ve verbal rating skala (VRS) kullanarak belirlemektir.
Metod: Tüm kraniyotomi hastalarına total intravenöz anestezi uygulandı. Tüm hastaların yaşı, kilo, boy, cinsiyet ve insizyonal bölgeleri (supratentoriyal veya infratentoriyal), operasyon nedeni (vasküler veya tümör) ve operasyon süreleri kaydedildi. Tüm hastaların kalp hızı, sistolik ve diastolik kan basınçları, Ramsay sedasyon skorları değerlendirildi ve cerrahiden sonrası 0., 30. ve 60. dakikalarda PACU unitesinden taburcu olana dek kaydedildi. Cerrahi öncesinde veya sonrasında bilinci kapalı olanlar, sınırlı kooperasyonu veya kognitif disfonksiyonu olanlar dışa bırakıldı.


Anahtar Kelimeler: Postoperatif ağrı, kraniyotomi, cinsiyet etkisi

INTRODUCTION
It has been suggested that, after neurosurgical procedures, especially following craniotomy, pain intensity of the patients, is typically between mild to moderate[6]. There are a few prospective studies about postcraniotomy pain management in the literature, most of the studies were performed retrospectively or as a questionnaire type.

Although it's known that craniotomy and most of neurosurgical procedures cause less pain than other surgical procedures, recent studies stated that postoperative pain intensity in craniotomy patients had increasing trends[2,7,10]. Early correct neurological examination especially following craniotomy, provides the recognition of surgical complications such as intracerebral hematoma which can precipitate loss of consciousness and increases the morbidity. Therefore, recovery after anesthesia should be quick and postoperative pain management should not have any sedative effects on the patients.

The aim of this study was to investigate the quality and quantity of the pain after craniotomy and it's relation with gender, age, weigth, incisional area and craniotomy causes (vascular or tumor).

MATERIAL AND METHODS
After getting approval from the Institutional Review Board, informed written consent was obtained from conscious and cooperative patients scheduled for elective intracranial surgery. Unconscious patients with limited cooperation and impaired cognitive functions before or after operation were excluded from the study.

One hundred eight patient were included in this study. Before surgery, all patients were informed about a visual analogue score (VAS; 0 – no pain, VAS; 10 - unbearable pain) and a verbal rating score (VRS; 0: no pain, VRS; 1: mild pain, VRS; 2: withstanding pain, VRS; 3: severe pain). Baseline patients' demographics and other data (age, weight, height, gender, incisional location 'supratentorial or infratentorial', surgical pathology 'vascular or tumor'), American Society of Anesthesiology status (ASA PHYSICAL STATUS CLASSIFICATION SYSTEM: ASA I: healthy patient, ASA II: patients have mild to moderate systemic disease, ASA III: Patients have severe systemic disease that limits activity, ASA IV: Patients have severe systemic disease that
limits activity and is a constant threat to life), Body Mass Index (BMI- kg.m$^{-2}$) were recorded. Intravenous and intra-arterial access was established before induction, and routine monitoring electrocardiogram (ECG), non-invasive blood pressure (NIBP), peripheral oxygen saturation (SpO2), end tidal carbon dioxide pressure (ETCO2) were applied. General anaesthesia was induced with thiopental (5 mg kg$^{-1}$ i.v) and fentanyl (2 mcg kg$^{-1}$ i.v). Endotracheal intubation was facilitated with rocuronium (0.6 mg kg$^{-1}$). For maintenance of anesthesia 0,1- 2 mg kg h$^{-1}$ propofol, 0,15-1,00 mcg kg min$^{-1}$ remifentanyl intravenous infusions were used and rocuronium (0,15 mg kg$^{-1}$ i.v) was delivered when necessary. The patients were ventilated by using volume controlled mode with 50% oxygen- 50% air mixture. Heart rate (HR), non- invasive blood pressure (NIBP), peripheral oxygen saturation (SpO2) and additional anesthetic medications were recorded with five minute intervals. As soon as the last surgical suture was put, anesthesia was ended and muscle relaxation was reversed.

Patients first cooperation time determined as 0. minute (min). The pain was assessed with a VAS and a VRS scales; heart rate, systolic and diastolic blood pressure, as well as alertness state according to Ramsey sedation scale was assessed and recorded. Ramsay sedation scale is used to assess the level of sedation of a hospitalized patients. The scale, from 1 to 6, describes a patient as follows:

1- anxious and agitated or restless, or both,
2- co-operative, oriented, and calm, 3- responsive to commands only, 4- exhibiting brisk response to light glabellar tap or loud auditory stimulus, 5- exhibiting a sluggish response to light glabellar tap or loud auditory stimulus, 6 -unresponsive.

These measurements were repeated at 30., 60. min and during the discharge from the Postanesthetic Care Unit (PACU).

Statistical evaluation performed by Biostatistics Department of Ege University. The pain scores were evaluated by Kruskal-Wallis test, connection between vital signs and pain scores with Friedmann test, evaluation between score for time zones with Wilcoxon test, demographic data and operative data with Chi-square test and differences parameters among data with Mann-Whitney U test. Significance level was set at p < 0,05.

RESULTS

Demographic characteristics of the patients are shown in Table 1. Analgesic requirements of the patients: Pain free patient ratio was 53. 7 % (n= 58) at first measurement at 0 min, 63 % (n= 68) at second measurement and 93. 5 % (n= 101) at third measurement.

There were statistically significant difference between 0 min and 30. minute's VAS and VRS scores. There were also statistically significant difference between 0 min and 1. hour's VAS and VRS scores (Graphic 1) (p<0,05). Systolic and diastolic pressures at 0. min were significantly decreased when compared with at 30. min and 60 min measurement (Table 2) (p<0,05). In women at 0. min and 1. hours VAS- VRS scores were higher than in men's VAS- VRS scores (p<0.05). There was no significant differences at 30. min VAS- VRS scores between men and women (Table 3).
There were no significant differences in VAS- VRS scores of the patients related with supratentorial or infratentorial surgical approach. There were no significant differences between VAS- VRS scores according to the patients’ surgical pathology (vascular or tumor) at all measurement times. There was no significant difference in VAS- VRS scores of the patients according to ASA physiologic status.

**Table 1. Demographic characteristics of the patients as (Mean ±SD)**

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>Age (Years)</td>
<td>49.0 ±13.0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>63 (% 58)</td>
</tr>
<tr>
<td>Men</td>
<td>45 (% 42)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165± 9.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72± 11.0</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>26± 4.0</td>
</tr>
<tr>
<td>Duration of surgery (hours)</td>
<td>3.12 ± 1.08</td>
</tr>
</tbody>
</table>

* (p< 0.05) There were statistically significant difference between 0 min and 30 minute's VAS and VRS scores. There were also statistically significant difference between 0 min and 1. hour's VAS and VRS scores. (Graphic 1).

**Graphic 1: Changes in VAS and VRS scores of the patients.**
Table 2: Hemodynamic data (heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>SAP</th>
<th>DAP</th>
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<tbody>
<tr>
<td></td>
<td>(beat/min)</td>
<td>(mmHg)</td>
<td>(mmHg)</td>
</tr>
<tr>
<td>Preoperative</td>
<td>89±16</td>
<td>138±21</td>
<td>77±14</td>
</tr>
<tr>
<td>Intraoperative</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0. min</td>
<td>87±13</td>
<td>139±22*</td>
<td>86±14*</td>
</tr>
<tr>
<td>30 min</td>
<td>85±13</td>
<td>134±20</td>
<td>82±11</td>
</tr>
<tr>
<td>1 hrs</td>
<td>81±11</td>
<td>129±17</td>
<td>79±9</td>
</tr>
</tbody>
</table>

*(p<0.05) Systolic and diastolic pressures at 0. min were significantly decreased when compared with at 30. min and 60 min measurement (Table 2).

Table 3: Male or Female patients and changes in VAS- VRS scores (mean± SD).

<table>
<thead>
<tr>
<th></th>
<th>0.min</th>
<th>30.min</th>
<th>60.min</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.22±2.29</td>
<td>3.22±1.97</td>
<td>2.53±1.05</td>
</tr>
<tr>
<td>Female</td>
<td>4.40±2.47</td>
<td>3.63±1.84</td>
<td>2.73±1.15</td>
</tr>
<tr>
<td>VRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.07±1.00*</td>
<td>1.16±0.87</td>
<td>0.93±0.53*</td>
</tr>
<tr>
<td>Female</td>
<td>1.63±1.08*</td>
<td>1.35±0.90</td>
<td>2.05±0.28*</td>
</tr>
</tbody>
</table>

*(p<0.05) In women at 0. min and 1. hours VAS- VRS scores were higher than in men’s VAS- VRS scores. There was no significant differences at 30. min VAS- VRS scores between men and women (Table 3).
DISCUSSION

In our prospective study about postoperative early pain following craniotomy have compared with other study results that postcraniotomy pain level were mild or moderate. In our study, the average pain scores after craniotomy were moderate according to patient’s VRS scores and disturbing for VAS scores. During postoperative period, 53% of the patients did not complain about any pain at 0. min and they did not need any analgesic treatment during study period. This percentage is higher than results of the other studies in recent years. At 30th and 60th minutes of postoperative period we observed statistically significant decrease in VAS and VRS scores of the patients. We think that relatively low VAS and VRS scores obtained in our patients are related with deeply injected local anesthetic around surgical incisional area. The procedure of local anesthetic infiltration, significantly decreased VAS and VRS scores of the patients during postoperative period.

We found very different pain scores than other retrospective studies. At the former studies related with postcraniotomy pain, the incidence of post craniotomy pain was reported as low as 18%. Benedittis et al. reported postoperative pain incidence of the patients as 63, 6% in their study.

Similarly Irefin et al., in their retrospective study, found that 84 % of 52 patients after elective craniotomy had moderate or severe pain. In these studies they didn't use any local anesthetic infiltration during pre- and postoperative periods. We suggested that lower percentage of (43,4 %) moderate or severe pain scores in our study is related with local anesthetic infiltration around surgical area. Tuchinda injected 0,5% and 0,25% bupivacaine with 1/200,000 adrenaline to all skull nerves (supratrochlear, supraorbital, zygomaticotemporal, auriculotemporal, great auricular, occipital and suboccipital nerves). He found that average blood pressure was lower in local anesthetic group but there wasn't any significant differences in heart rate records.

In Tuchinda’s study, intravenous morphine PCA was used for pain treatment during postoperative period; but there was no significant difference in total morphine consumption between groups. Main difference of this study is the local anesthetic injection to all cranial nerves except for surgical incisional area. Local anesthetic mixture was injected around incisional area including periosteum in our study. Total amount and concentration of local anesthetic as well as the type of local anesthetic agent that used have also important effects on quality and duration of perioperative analgesia.

We think all of these factors may have important effects on difference between our results and Tuchinda’s results. For achieving postoperative analgesia, Nguyen et al. injected 0,75 % bupivacaine with 1/400,000 adrenaline around incisional area in patients undergoing supratentorial craniotomy. During the postoperative follow-up period of the patients, especially at the 1st hour, there was a significant (50%) decrease in pain scores. They also reported that there was a significant decrease in VAS and VRS scores during the first 12 hours follow-up period. And postoperative analgesia prolonged to 48 hours. We think that, the results of this study, support the efficacy of local anesthetic infiltration around the surgical area like results of our study. In another study 0,75% ropivacaine was injected around the scalp area at the end of surgical session and this significantly decreased the severity of postoperative pain scores. Local anesthetic infiltration may cause preventive postoperative analgesic effect and may reduce the need for usage of non-steroidal anti-inflammatory drugs (NSAIDs) during postoperative period. Because of the effective pain control that
was achieved with local anesthetic infiltration in our study, we think that postcraniotomy pain might arise from scalp, soft tissues and periosteum.

Stoneham et al.\(^{(18)}\) had reported that postcraniotomy pain was treated inefficiently in England according to the results of their questionnaire survey obtained from 183 neuroanesthetists. De Benedettis et al.\(^{(2)}\) identified that 60% of craniotomy patients experienced postcraniotomy pain and 2/3 of them described that postcraniotomy pain was moderate or severe. This percentage was different from the old post craniotomy pain incidence as 5-15% assessed before. We observed moderate and severe postcraniotomy pain in patients scheduled for craniotomy, according to their VAS and VRS scores. Our results are located between the traditional „craniotomy causes low pain“ concept and recent opinion which claims „2/3 of patients experienced with severe post craniotomy pain“ in the literature. We think that, the cause of the main difference of our prospective study results than other studies was related with local anesthetic infiltration around the surgical area.

In a retrospective study, intraoperative fentanyl infusion was used during craniotomy and intravenous morphine delivered for postoperative analgesia at the end of the surgery\(^{(4)}\). Than, there was a prolonged analgesic effect spilled over to postoperative period and patients experienced less postoperative pain following craniotomy. Quiney et al.\(^{(15)}\) also reported the postoperative moderate and severe pain in 18% of patients. Similarly as in our study they had applied local anesthesia around incisional area. But as distinct from this study we did not use fentanyl, alfentanyl or inhalation agent with postoperative prolonged effect. We used remifentanil infusion for achieving intraoperative analgesia with 5-9 minutes of half-life and this agent could not have prolonged effect during postoperative period. The low levels of moderate and severe pain as 18% in Quiney et al.'s study\(^{(15)}\) may be explained by these factors.

Postoperative pain may cause an increase in the sympathetic activity. This haemodynamic response can lead to hypertension and postoperative intracranial hematoma. In our study the hemodynamic data, HR, SAP and MAP values, were similar preoperatively and at 0. min. This situation may be explained as patients did not feel too much pain. HR, MAP and SAP significantly decreases at 30\(^{th}\) and 60\(^{th}\) min. This decrease may be explained with patients' emotional comfort, less pain and sufficient effect of routine postoperative analgesia. It may be criticized that local anesthetic infiltration can affect the pain scores but it must be kept in mind that a hypertensive period can cause intracranial hematoma postoperatively.

Different pain scores which was obtained following craniotomy and experimental researches can be explained by many factors. Noxious stimuli of supratentorial structures cause pain in anterior part of the cranium. And stimuli of cerebellum's tentorium cause pain in inferior parts of the cranium. Cranial bones are not sensitive for pain but periosteum and arterial structures are sensitive\(^{(5)}\).

The sensitive part of cranial nerves are located infratentorially so it was thought that infratentorium is more painful than the other parts of the cranium. Benedettis et al.\(^{(2)}\) reported more pain after suboccipital and subtemporal approaches. As well as differences of body part, Dunbar et al.\(^{(4)}\) had suggested that pain arised from frontal craniotomy is more severe than the pain arised from other parts of cranium. However Irefin et al.\(^{(9)}\) identified that localization of craniotomy was not an important factor for postcraniotomy pain. We did not find any statistical differences between postoperative pain scores after supratentorial and infratentorial craniotomy. There are much more muscle mass in temporal and suboccipital area so this might cause more postcraniotomy
pain\(^{(14)}\). Tuchinda\(^{(13)}\) reported that there were no difference in postoperative pain and location of craniotomy. He explain that this finding was related with local anesthetic infiltration.

Irefin et al.\(^{(9)}\) followed up 28 infratentorial and 53 supratentorial craniotomy patients within 24 hours and they reported no difference in pain scores between incisional areas. Fabling et al.\(^{(5)}\) in their retrospective study reported that infratentorial craniotomy is more painful than supratentorial craniotomy. Thibault et al.\(^{(19)}\) also reported less pain and need for analgesia after frontal craniotomy than posterior fossa surgery. At the same study they also identified less postoperative pain and reduced need for postoperative analgesia following frontal incision, than temporal or suboccipital approaches. Irefin et al.\(^{(9)}\) reported more pain in infratentorial area. They explained this with anatomic position of pericranial muscles. In the same study, there were no differences between aneurysm surgery and other frontotemporal craniotomy procedures. But this study was a retrospective study and follow-up was performed by nurses using only VRS scores.

We did not find any correlation between location of surgical incision and pain scores like Irefin et al.\(^{(9)}\). Our results may be related with the effects of local anesthetic infiltration and our postoperative analgesic protocol.

The gender difference is also an important factor discussed in pain perception. Men and women difference also arises from cultural factors, pain prevalence in case of illness, current expression of pain and drug response difference\(^{(11,12,16,17)}\). Nonetheless, prevalence of pain is more frequent in women than men\(^{(16)}\). Benedettis et al.\(^{(3)}\), found high incidence of pain in young and female patients, they suggested that gender and age were very important factors in postoperative pain in patients undergoing craniotomy. However, there is no consensus about correlation between pain perception and gender. Thibault et al.\(^{(19)}\), in their retrospective study with 299 patients, reported that the need of analgesia decreases as the age increases. In this study they reported that gender doesn’t have any role on postoperative pain. In man was 26.6%. The results of our study compared with the point of view that postcraniotomy pain is significantly higher in women.

According to the data in literature, women are more sensitive to pain than men. There are many factors that may explain this difference: biological, sociological, psychological variables and disease prevalence and/or clinical pain condition, pain perception is from kappa receptors in women and from mu receptors in men, also molecular, genetic profile, social, psychoclogical, cultural and experiential prejudices. Hormonal variations, puberty, period of productivity and menstrual cycle are the other factors in pain perception in women.

Thibault et al.\(^{(19)}\) in their study which contains 299 patients, reported that the pain and need for analgesia decreases with increasing age. Benedettis et al.\(^{(3)}\) in their study which performed with 37 patients, suggested that age is the most important factor in pain perception. The elderly patients tolerate the pain better\(^{(8,20)}\). If the pain perception decreases with age there may be a relationship with age-related changes like visual and autonomic system differences\(^{(20)}\). Nonetheless there are evidences for pain perception changing with age\(^{(8,20)}\). We did not detect any age correlation with pain. We think it was related with the age limit which was 65 in our study. We didn't find any statistically significant correlation between duration of surgery and BMI with VAS or VRS values.

Our prospective study about postcraniotomy pain showed that craniotomy causes mild to moderate pain, and women are more sensitive to this type of pain. Consequently, there are very few prospective studies about postcraniotomy
pain and most of them are retrospective or questionnaire studies. The prospective studies have also insufficient number of cases. We think that more prospective studies should be made with large case numbers in this subject because pain mechanism and factors affecting it are still not clear and need to be investigated. We can nevertheless confirm that there are some limitations of this study. The current study was unable to analyse these variables: the size of the cranial incision of the patients, the preoperative habits of the patients for painkillers, their former “headache” frequency history, the amount of collection from surgical drain after the surgery.

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