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Original Article

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ABSTRACT

Objectives: Multi-modal analgesia is achieved by the combined use of analgesic agents acting on different parts of the pain pathway. This study aims to compare the effects of epidural analgesia and periarticular injection on postoperative pain for 48 hours following total knee arthroplasty (TKA) and on the early functional outcomes.

Design: Single-center, prospective, randomized-controlled, and double-blind study

Setting: Health Sciences University, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

Subjects: Patients who underwent unilateral TKA included the study.

Intervention(s): The patients were divided into two groups: epidural morphine (Group E) and periarticular injection including 100 mL cocktail solutions (bupivacaine, adrenaline, dexmedetomidine, magnesium sulphate, methylprednisolone, morphine and normal saline) (Group P).

Main outcome measure(s): Our primary outcomes were Visual Analogue Scale (VAS) pain scores, Dynamic Visual Analogue Scale (DVAS) pain scores, and consumption of analgesics. Secondary outcomes were maximum range of motion (ROM), and side effects.

Results: A total of 24 and 27 patients were analyzed in Group P and Group E, respectively. Group P had significantly lower VAS and DVAS scores within the first 48 hours, lower amount of consumed analgesics at 24 and 48 hours, higher ROM values on 2 and 3 days, and more severe nausea, vomiting, and itching at 12 and 24 hours.

Conclusion: Our study results show that periarticular injection with multi-modal drugs in TKA is superior to epidural analgesia with lower VAS-DVAS scores, less analgesic consumption, fewer side effects, and improved ROM.

KEYWORDS: periarticular injection; epidural analgesia; dexmedetomidine; magnesium sulfate; morphine

INTRODUCTION

Total knee arthroplasty (TKA) is one of the frequent major orthopedic surgeries[1]. Postoperative pain is a major concern for patients and can directly affect functional recovery[2,3]. In the postoperative period, good pain control increases patient satisfaction, facilitates rehabilitation, and shortens the length of hospital stay[3]. Early mobilization also decreases the risks of complications, such as deep venous thrombosis, pulmonary embolism, pneumonia, and urinary retention. Early rehabilitation can be also possible with early recovered maximum range of motion (ROM) postoperatively[4]. Analgesia following TKA is usually multi-modal and involves the use of intravenous (IV) opioids, peripheral nerve block, epidural analgesia, joint or synovial opioid or local anesthetics injection and use of oral analgesics[1,3,5]. Although there is no consensus yet on what the gold standard for postoperative pain is[6], there has been a tendency toward multi-modal approaches with regional anesthesia to minimize opioid consumption and to avoid side effects associated with opioids[7]. Post-TKA liposomal bupivacaine has been also in use in recent years[8]. Several prospective studies have demonstrated that liposomal bupivacaine neither improves the quality of postoperative pain, nor improves the quality of recovery of these patients[8,9].

In the present study, we aimed to compare the effect of epidural morphine analgesia and periarticular injection on postoperative pain, analgesic consumption, and early period ROM following TKA.

SUBJECTS AND METHODS

Patients

A written informed consent was obtained from each patient. The study protocol was approved by the Local Ethics Committee and Australian New Zealand Clinical Trials Registry (Ref: ACTRN12616000226404). The study was conducted in accordance with the principles of the Declaration of Helsinki. This single-center, prospective, randomized-controlled, and double-blind study included a total of 60 patients who were older than 18 years old and underwent unilateral TKA with a knee prosthesis due to primary varus knee osteoarthritis. Exclusion criteria were as follows: being allergic to the drugs used, previous knee surgery or bilateral total knee prosthesis, severe liver and kidney failure, stroke, coronary heart disease, cognitive impairment, being uncooperative or under chronic opioid treatment, a body mass index (BMI) of >40 and regional anesthesia contraindication. Patients in whom an epidural catheter was unable to be placed, who developed epidural catheter migration, in whom general anesthesia was switched, who had cardiopulmonary arrest, and whose postoperative epidural catheter dislocated were also excluded (Figure 1). All patients were randomly divided into two groups using a sealed envelope system. Patients and the anesthesiologist who evaluate postoperative pain were blinded the study.

Anesthesia Management

For premedication, 0.01-0.02 mg/kg IV midazolam (Zolamid®, Defarma, Ankara, Turkey) was administered. An 18G Touhy needle (Epifix Standart®, Egemen, Izmir, Turkey) was placed into the L_{3-4} or L_{4-5} interval spaces at the middle in the sitting position to reach the epidural space with loss of resistance method. The catheter was, then, advanced through a 27G Quinke spinal needle into the subarachnoid space and bupivacaine 3 mL 0.5% spinal heavy (Spinal Heavy Bustesin®, Vem, Ankara, Turkey) was administered intrathecally. The epidural catheter was advanced 4-5 cm further. Following spinal anesthesia, sensory block level was determined by pinprick test, and motor block level was determined by the Bromage score (Grade 0: No motor block; Grade 1: Inability to raise extended leg, able to move knees and feet; Grade 2: Inability to raise extended leg and move knee, able to move feet; Grade 3: Complete block of motor limb). The surgical procedure was initiated, when the sensory block reached T_{10} level and Bromage score was 2.

Surgery Management

All operations were performed by a single surgeon. All operations were conducted under pneumatic tourniquet. The tourniquet pressure was set to a level that it would be 150 mmHg higher than the systolic blood pressure of the patient. An anterior incision approach was used in all patients. To reach the joint, medial parapatellar arthrotomy was performed. Then, in accordance with the technique which was described by Sahin *et al*.[10], a cemented posterior-stabilized and fixed-insert total knee prosthesis

(GENESIS II, Smith&Nephew Inc. Memphis, USA) was applied in all patients. A drain was placed in all patients postoperatively.

Procedure of Periarticular Analgesia (Group P, n=30)

A cocktail of 100 mL containing 20 mL of 0.5% bupivacaine (Bustesin®, Vem, Ankara, Turkey), 0.6 mL of 1 mg/mL of adrenaline (Adrenalin®, Oesel, Istanbul, Turkey), 1 mL of 100 µg/mL dexmedetomidine (Precedex®, Meditera, Izmir, Turkey), 4 mL of 8.4% magnesium sulphate (Magnezyum Sulfat®, Biofarma, Istanbul, Turkey), 4 mL of 10 mg/mL methylprednisolone (Prednol-L®, Mustafa Nevzat, Istanbul, Turkey), 0.5 mL of 10 mg/mL morphine (Morphine HCl®, Galen, Istanbul, Turkey), and 69.9 mL normal saline solution were prepared into two of 50 mL injectors. In the administration of injections, the areas with increased neurosensory and mechanoreceptors were selected, as described by Dye *et al*. [11] based on the technique described by Guild *et al*.[12], 60 mL of the solution was administered to the medial retinaculum, medial collateral ligament, medial meniscocapsular component, at the attachment site of posterior cruciate ligament to tibia, at the attachment site of the anterior cruciate ligament to femur, lateral retinaculum, lateral collateral ligament and lateral meniscocapsular junction, following the tibial and femoral incisions. The injection was applied to each spot at one time not to exceed 2-3 mL and to avoid overflowing of the active ingredient from the soft tissue. Following placement of the tibial and femoral components, the remaining 40 mL of the cocktail was administered to the suprapatellar pouch, quadriceps tendon, patellar tendon, and patellar fat pad.

Epidural Analgesia Managemenet (Group E, n=30)

A total of 10 mL solution containing 3 mg morphine (3 mL) and normal saline was administered from the epidural catheter to all patients, before the incision was closed.

Postoperative Analgesia Management

A patient-controlled epidural analgesia (PCEA) (CADD-Legacy® PCA, Smiths Medical, St Paul, USA) device was connected for 48 hours. A total of 160 mL of epidural solution containing 40 mL of 0.5% bupivacaine + 10 mL of 500 µg of fentanyl + 110 mL of 0.9% NaCl was prepared. Without basal infusion, the bolus dose was set at 10 mL, the lock duration was set at 20 min, and the hourly limit was set at 30 mL. A special program for postoperative rehabilitation was not performed, and all patients were instructed to make knee ROM exercises as much as they could tolerate pain. In the first postoperative day, all patients were mobilized with full load and with the assistance of a walker.

Primary Outcomes

To evaluate the postoperative pain level, the Visual Analogue Scale (VAS) (where 0=no pain, 10=worst imaginable pain) was used at rest, while the Dynamic VAS (DVAS) was used to evaluate pain during exercise. Postoperative pain was assessed at 2, 4, 8, 12, 24, 36, and 48 hours by another anesthesiologist. Tramadol HCl (Tramosel®, Haver, Istanbul, Turkey) 50 mg IV was administered as a

rescue analgesic in patients with a VAS score of >3 whose pain did not relieve, despite bolus dosing. Total analgesic consumption and rescue analgesic doses were also added for 48 hours.

Secondary Outcomes

Patient characteristics were recorded. Of the patients, total ROM between the active maximal flexion and maximal extension was evaluated on postoperative 1, 2, and 3 days, and complications which developed within 48 hours were also noted. Requirement for rescue analgesia and side effects, including nausea, vomiting, and itching during 48h follow-up were also evaluated.

Statistical Analyses

The power calculation for the present study is based on an effect size of 0.75 with an alpha (α) value of 0.05. The required sample size to obtain a power of 0.8 under these assumptions was 23 for each group. Statistical analysis was performed using SPSS version 21.0 software (Statistical Package for the Social Sciences, Armonk, NY, USA). The Shapiro-Wilk test was used to analyze normal distribution of the data. T-test was used to compare two groups with normally distributed data, while the Mann-Whitney U test was used to compare more than two groups with abnormally distributed data. The Wilcoxon sign-rank test was used to compare the dependent samples. In the analysis of repeated measures, percentage changes from baseline were calculated and compared using these values. The Pearson's chi-square, Fisher's exact chi-square, and Fisher-Freeman-Halton tests were used to analyze categorical data. A *p* value of 0.05 was statistically significant.

RESULTS

Of 60 patients included in the study, 51 were evaluated (Figure 1). There was no significant difference in demographic characteristics between the two groups (Table 1).

The VAS scores in Group P were significantly lower than the baseline during the first 48 hours ($p<0.05$) (Figure 2). The DVAS scores at 24, 36, and 48 hours were also significantly lower in Group P ($p<0.05$) (Figure 3). The amount of analgesics consumed with the PCEA device was significantly lower in Group P during 48 hours ($p<0.05$) (Table 2). The need for rescue analgesics were not significantly between the two groups ($p>0.05$) (Table 2).

There was no significant difference in the ROM values on first day ($p>0.05$), however, the ROM values were significantly higher on 2 and 3 days in Group P ($p <0.05$) (Table 3).

The rate of nausea, vomiting, and itching at 12 and 24 hours was significantly higher in Group E ($p<0.05$) (Table 4).

Group P significantly predicted overall mean VAS scores ($p < 0.001$) while the age, sex and BMI were not significant (Table 5).

DISCUSSION

In this prospective, randomized trial, we evaluated the efficacy of epidural analgesia and single administration of a multi-modal periarticular injection for pain control following TKA. In the periarticular injection group, the VAS and DVAS scores were significantly lower within the first 48 hours, the amount of epidural analgesics consumed at 24 and 48 hours were significantly lower, the ROM values on 2 and 3 days were significantly higher, and nausea, vomiting, and itching at 12 and 24 hours were significantly lower.

Currently, several pain control modalities are in use for the management of TKA; however, opioids and patient-controlled analgesia morphine are the main compounds in primary postoperative relief thanks to their efficacy in relieving moderate-to-severe pain [13]. However, their sole use has been falling out of favor due to their potential side effects and intolerance, particularly in the elderly population with multiple comorbidities[14]. Epidural analgesia including opioids and local anesthetic agents were suggested as the gold standard for postoperative pain control by Bromage *et al*[15]. In a meta-analysis comparing epidural analgesia and paranteral opioids, it was shown that epidural analgesia provided better pain control for all surgical types[16]. However, lumbar epidural analgesia has been also associated with poor postoperative mobility and complications, such as epidural hematomas and perioperative hypotension[13,17]. In today's practice, periarticular injection is frequently used for pain management at the surgical site of TKA to avoid potential complications of other nerve blocks [13].

In the literature, agents used in periarticular injections vary, and the amounts of cocktail ranges between 20 and 150 mL[18-24]. In our study, we used 100 mL of cocktail. To maximize the benefit from the combination effect of the drugs, we used bupivacaine, adrenaline, dexmedetomidine, magnesium sulphate, methylprednisolone, and morphine combination. To the best of our knowledge, there are few studies on the periarticular use of dexmedetomidine and magnesium[22,23]. We, therefore, believe that our study contributes to the literature data, as this is the first study which combined dexmedetomidine and magnesium sulphate in the periarticular use.

Tsukada *et al*. [25] compared periarticular injection with epidural anesthesia. They administered ropivacaine (200 mg) and morphine infusion (8 mg) in the epidural analgesia group and 60 mL of cocktail (ropivacaine, morphine, epinephrine, methylprednisolone, ketoprofen, and saline) in the periarticular injection group. In the aforementioned study, significant difference was observed between the VAS scores, and no significant difference was observed between the DVAS scores and the use of rescue analgesics during the first three days[25]. Our results are different with these results. In the study comparing epidural analgesia (ropivacaine infusion) with intraarticular analgesia (intraarticular infusion after incision site infiltration) by Andersen *et al*. [24], the VAS and DVAS scores and morphine consumption were found to be significantly higher in the epidural group during 72 hours. Our results are consistent with these results. However, different from our study, the aforementioned authors performed intraarticular infusion and evaluated morphine consumption. In the regression analysis of another study, postoperative pain scores after TKA were found to be higher in females and younger patients[26]. In our study, these two variables were not found to be significantly correlated, while only Group P variables were significant. In a study

comparing epidural analgesia (bupivacaine + fentanyl) and intraarticular infusion (bupivacaine + ketorolac), there was no significant difference in the VAS scores during 48-hour follow-up[27]. In addition, Niemelainen *et al*. [20] compared the periarticular injections containing 100 mL multi-drug medications and those containing 100 mL of saline. The multi-drug injected group required significantly less morphine for 48 hours. In our study, 48-hour analgesic consumption was found to be significantly lower in the periarticular group. In a meta-analysis carried out by Teng *et al*. [28], periarticular injection with multi-modal drugs significantly improved pain relief and straight leg raise in the early postoperative period.

On the other hand, the majority of previous studies in the literature were not designed as blinded studies[24,25,27]. One of the strengths of our study is, therefore, that it was carried out as a double-blind study which refers to that the investigator who assessed the patient and pain was blind to the study. Since the PCEA was applied to all patients, the investigator who evaluated postoperative pain remained blind to the study.

In a study comparing epidural morphine and periarticular injection, nausea was significantly lower on postoperative 24 hours in the periarticular group, although no significant difference in complications on other days was observed [25]. In our study, nausea, vomiting, and itching were significantly higher at 12 and 24 hours in the epidural analgesia group, unlike the aforementioned study. Andersen *et al*. [24] compared intraarticular and epidural analgesia, and did not report any toxic symptoms associated with local anesthesia. There is also a meta-analysis reporting complications such as nausea and vomiting due to epidural analgesia[16]. In another study comparing epidural analgesia and intraarticular infusion, hypotension, paresthesia, and abdominal distension were observed more often in the epidural group[27]. Tsukada *et al*. [25] reported the rate of transient peroneal nerve palsy was higher in the periarticular injection group. In our periarticular group there was no transient peroneal nerve palsy.

Furthermore, a study comparing epidural morphine and periarticular injection showed that flexion motion significantly improved in the periarticular injection group, although there was no significant difference in the extension angle[25]. Milani *et al*.[18] compared the patients who were administered periarticular injection with ropivacaine and those with no periarticular injection, and found no significant difference in the ROM values between the two groups. In a study comparing epidural analgesia and intraarticular injection, the patients with intraarticular infusion were able to stand up earlier[27]. In addition, in a study comparing periarticular injections with levobupivacaine and the control group in which periarticular injection with saline was used, there was significant difference in the ROM values at 6 hours, but not at 24 and 48 hours[20]. In our study, the ROM values on 48 and 72 hours were significantly higher in the periarticular injection group.

Limitations

Nonetheless, this study has some limitations. First, plasma concentrations of bupivacaine was unable to be measured. Secondly, the results of this study are only limited to patients undergoing regional anesthesia and are unable to be generalized for general anesthesia procedures. Third, it is inadequate to provide information on the long-term effects of analgesia methods used. The effects of acute pain relief

following TKA on chronic pain and functional outcomes at one year can be the subject of another study.

CONCLUSION

Our study results show that as postoperative multi-modal analgesia in TKA, periarticular injection provides less complication and improved pain control with improved ROM than epidural analgesia. Therefore, we suggest that the multi-modal drug periarticular injection is an effective and safe method for postoperative analgesia in TKA.

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Authors' contribution to the manuscript:

Karasu: protocol/project development, data collection and, management, writing/editing.

Sahin: protocol/project development, data collection and, management, writing/editing.

Cansabuncu G: data collection, manuscript reviewing.

Yılmaz: data analysis, manuscript reviewing,

Cansabuncu S: data collection, manuscript reviewing,

Ozkaya: data analysis.

Conflict of interest: All authors declare that they have no conflict of interest.

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Table 1: Patient characteristics

Patient Characteristics	**Group P (n=24)**	**Group E (n=27)**	**p**
Age (year)*	65.92 ± 7.30	66.56 ± 7.88	0.766
Sex (Female) **	19 (79.2)	20 (74.1)	0.669
Height (cm)*	163.17±5.88	162.19±7.23	0.601
Weight (kg)*	77.71±13.22	74.15±10.37	0.287
ASA***			0.707
• **I**	3 (12.5)	5 (18.5)	
• **II**	21 (87.5)	21 (77.8)	
• **III**	0	1 (3.7)	

ASA: American Society of Anesthesiology *mean±standard deviation ** n, (%)

Table 2: Range of motion according to groups

ROM	**Group P (n=24)**	**Group E (n=27)**	**p**
1st day*	96.04±13.18	100.56±13.61	0.236
2nd day*	103.33±13.40	100.93±10.83	**0.001**
3rd day*	107.08±9.43	104.07±10.09	**0.002**

ROM: Range of motion *mean±standard deviation

Table 3: Analgesic usage profile of the groups

Analgesic usage profile	**Group P (n=24)**	**Group E (n=27)**	**p**
Amount of consumed analgesics (ml)*			
0-24 hours	147.91±26.20	171.85±32.82	**0.006**
24-48 hours	133.75±33.98	160.74±33.38	**0.003**
Requirement of rescue analgesics**	2 (8.3)	7 (25.9)	0.100

*mean±standard deviation, **n, (%)

Table 4: Side effects

Side effects	**Group P (n=24)**	**Group E (n=27)**	**p**
Nausea*			
12th hours	4 (16.7)	21(77.8)	**< 0.001**
24 th hours	2(8.3)	15(55.6)	**< 0.001**
48 th hours	0(0)	2(7.4)	0.492
Vomiting*			
12th hours	2(8.3)	18(66.7)	**< 0.001**
24th hours	1(4.2)	10(37)	**0.004**
48th hours	0(0)	0(0)	
Itching*			
12th hours	1(4.2)	21(77.8)	**< 0.001**
24th hours	1(4.2)	18(66.7)	**< 0.001**
48th hours	0(0)	4(14.8)	0.113

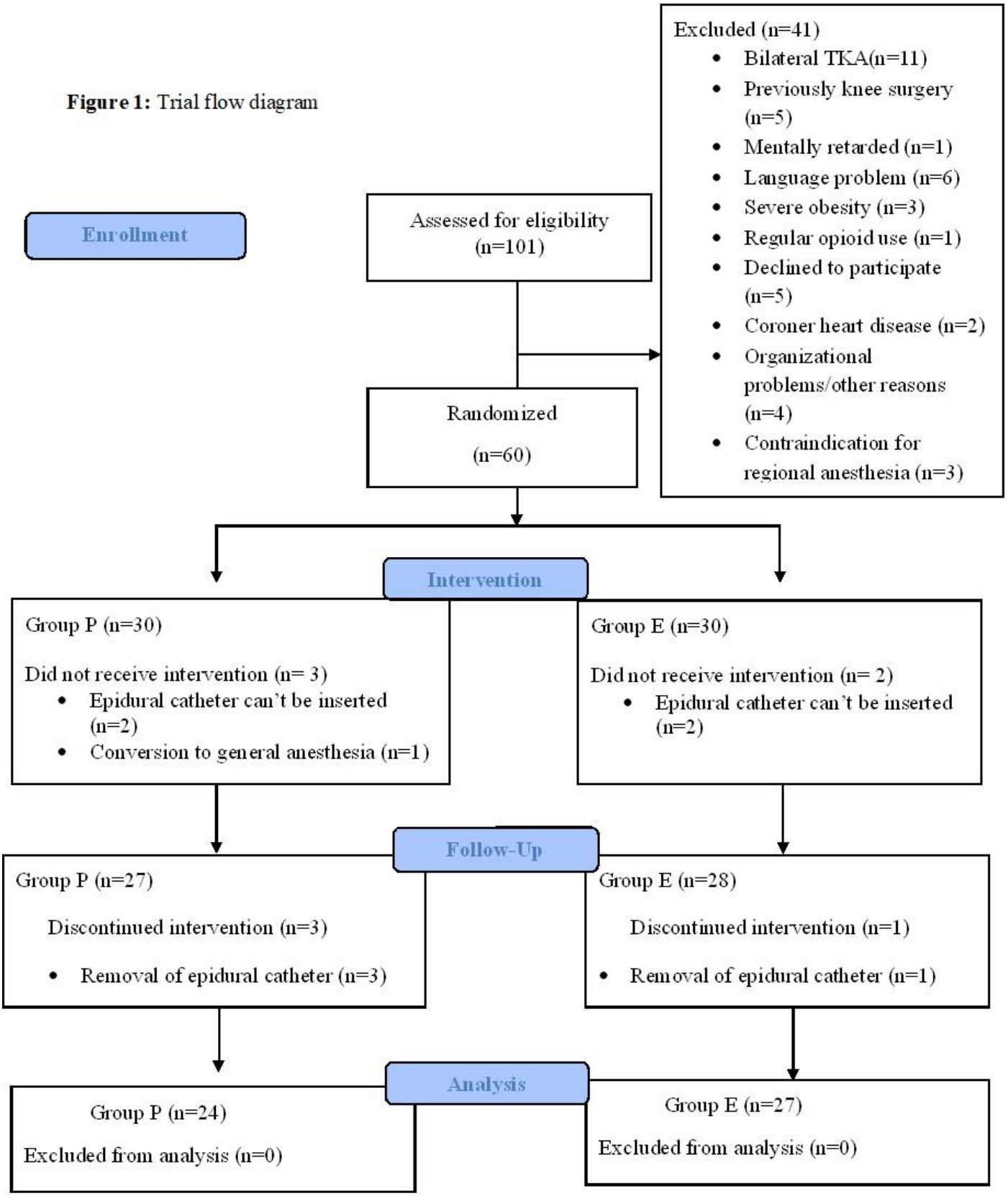
*n, (%)

Table 5: Multivariable regression analysis results for overall average VAS pain scores

VAS Pain Scores	**Coefficients**	**p**
Age	0.044	0.711
Male versus Female	0.026	0.818
BMI	-0.100	0.378
Group P versus Group E	0.709	**<0.001**

VAS: visual analogue scale; BMI: body mass index

Figure 1: Trial flow diagram



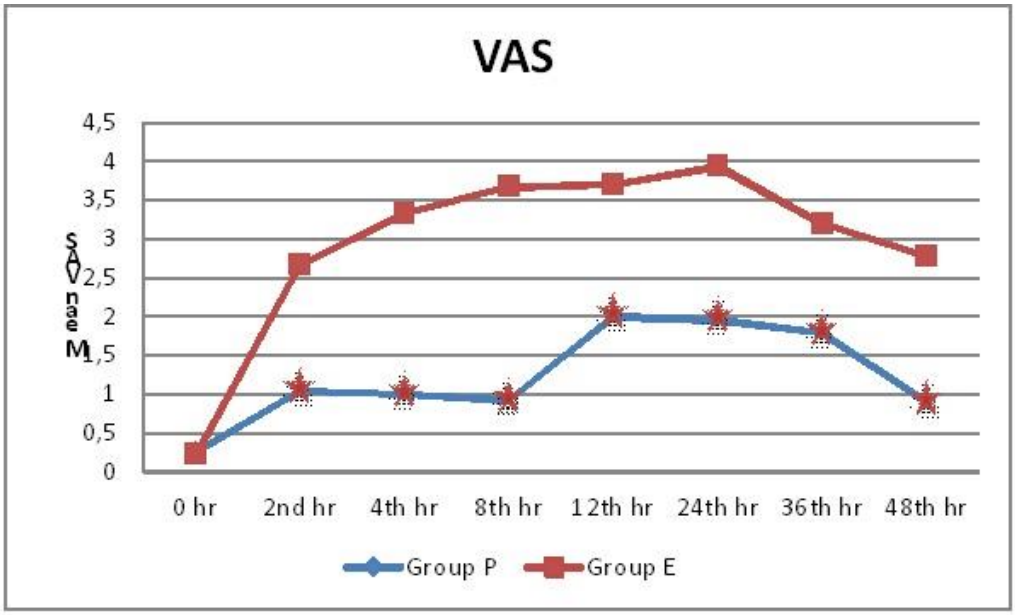


Figure 2: Mean values of Visual Analogue Scale (VAS) according to groups

* p <0.05

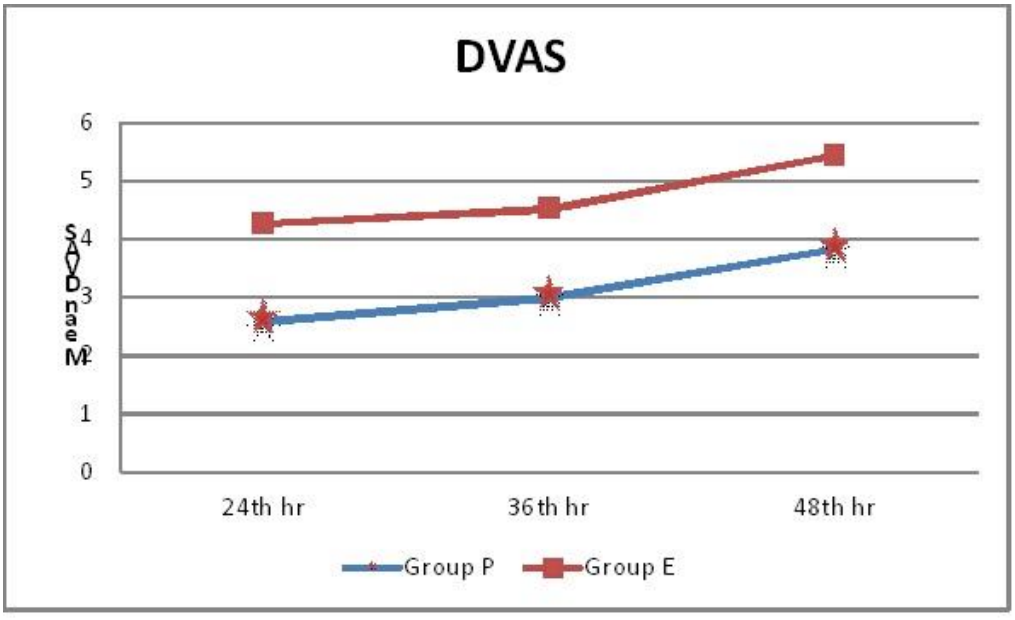


Figure 3: Mean values of Dynamic Visual Analogue Scale (DVAS) according to groups

* p <0.05