

Does Patient-Controlled Infraclavicular Perineural Dexmedetomidine Increase the Duration of Postoperative Analgesia?

Hasta Kontrollü İnfraklaviküler Perinöral Dexmedetomidin Postoperatif Analjezi Süresini Uzatıyor Mu?

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ABSTRACT

Objective: Peripheral nerve blocks are now used widely for postoperative analgesia and peripheral nerve catheters are widely utilized. Objective of this study was to investigate effect of perineural infusion of dexmedetomidine on the duration of postoperative analgesia retrospectively.

Material & Methods: A total of 60 patients aged between 18 and 65 years were included in the study. Group 1 received infraclavicular patient-controlled perineural bupivacaine (0.1 %). Group 2 received infraclavicular patient-controlled perineural bupivacaine (0.1 %) + dexmedetomidine (200 mic/100 cc). Blood pressure, pulse, peripheral oxygen saturation modified ramsay sedation scale, visual pain scores, total amount of analgesics were recorded at the 0, 30, 60, 90 minutes and 2, 4, 6, 8, 12, 24 hours.

Results: Systolic blood pressure was higher in Group 1 at the hour 6 (p: 0.007). Whereas, diastolic blood pressure was higher in Group 1 at the hours 4 and 6 (p: 0.000, p: 0.003). Heart rate was found to be higher in Group 2 at the hours 8, 12 and 24 (p: 0.004, p: 0.002, p: 0.002). Patients in Group 1 were found to significantly feel pain and need analgesics at the hours 4 and 6 (p: 0.002, p< 0.05). The mean number of patient requests for analgesia was 5.8±1.4 times in Group 1 and 2.2±0.4 in Group 2 (p<0,05). None of the patients developed sedation/neurological deficits.

Conclusion: Perineural infusion of dexmedetomidine combined with bupivacaine was found to increase the duration of postoperative analgesia, reduce 24-hour need for analgesia and have not any adverse effect at low doses.

Keywords: Patient-Controlled Analgesia; Perineural Dexmedetomidine infusion; Duration of Postoperative Analgesia

ÖZ

Amaç: Son zamanlarda postoperatif analjezi amaçlı periferik sinir blokları ve periferik sinir kateterleri yaygın olarak kullanılmaya başlanmıştır. Bu çalışmamızda; dexmedetomidinin perinöral infüzyonunun postoperatif analjeziye etkisini retrospektif olarak araştırmayı amaçladık.

Yöntemler: Distal üst ekstremitte cerrahisi geçiren, toplam 60 hasta çalışmaya alındı. Grup 1: infraklavikular hasta kontrollü perinöral bupivakain (0.1 %). Grup 2: infraklavikular hasta kontrollü perinöral bupivakain (0.1 %) + dexmedetomidin (200 mic/100 cc). 0, 30,60,90, 120. Dk ve 4, 6, 8, 12, 24, saatlerde kan basıncı, nabız, periferik oksijen saturasyonu, modifiye ramsey sedasyon skalası, visüel ağrı skorları, total analjezik miktarı kaydedildi.

Bulgular: Grup 1'de, 6. Saat sistolik kan basıncı, grup 2'ye göre yüksekti (p: 0,007). Diyastolik kan basıncı ise 4. ve 6. Saatlerde grup 1'de daha yüksekti (p: 0,000, p: 0,003). 8., 12. ve 24. Saatlerde kalp hızı grup 2'de daha yüksek bulundu (p: 0,004, p: 0,002, p: 0,002). 4. ve 6. Saatte grup 1'deki hastaların anlamlı olarak ağrı hissettikleri ve analjezik ihtiyaçları olduğu saptandı (p: 0,002, p: 0,000). Grup 2'de ilk ağrı hissedilen zaman 6. Saat olarak saptandı. Grup 1'de ortalama 5,8±1,4 defa analjezi ihtiyacı olmuşken, grup 2'de ortalama 2,2±0,4 defa analjezi ihtiyacı olmuştur (p: 0,000). Hiçbir hastada sedasyon / nörolojik defisit gözlenmedi.

Sonuç: Dexmedetomidinin bupivakainle beraber perinöral infüzyonunun postoperatif analjezi süresini artırdığı, 24 saatlik analjezi ihtiyacını azalttığı ve düşük dozlarda hiçbir yan etkiye neden olmadığı görülmüştür.

Anahtar Kelimeler: Hasta Kontrollü Analjezi; Perinöral Dexmedetomidin İnfüzyonu; Postoperatif Analjezi Süresi

INTRODUCTION

Regional anesthesia techniques have important advantages compared to general and systemic analgesia, including excellent pain control, reduced adverse effects and less length of stay in the post-anesthesia care unit(1-3). Peripheral nerve blocks don't only reduce the need for intraoperative analgesia, but they also provide effective analgesia in the postoperative period without significant systemic side effects(4).

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With the use of perineural catheters, early discharge is provided with postoperative analgesia(5). With the continuous infusion of local anesthetic through the catheter, pain control is provided with less opioid consumption and healing process is accelerated with patient satisfaction(6,7).

Adjuvant agents are often used in combination with local anesthetics in order to increase the duration and quality of the block in peripheral nerve blocks (8). Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist. It has several effects such as reduced blood pressure, sedation, sleep, analgesia and reduction of the memory loss and in shivering. Its administration alone or in combination has been tested(9-11) and also there are studies demonstrating that perineural administration of dexmedetomidine in combination with local anesthetics prolongs the duration of nerve block(12,13). However, there was no data related to the perineural infusion of dexmedetomidine in the literature.

In this study, we aimed to investigate effect of perineural infusion of dexmedetomidine added to bupivacaine on the duration of postoperative analgesia, 24-hour needs for analgesia, side effects of dexmedetomidine, ramsey sedation scale and neurological follow-up examination.

SUBJECTS AND METHODS

After approval was obtained from the ethics committee of Erzincan University (Decision No. 08/06) and the patient's consent, a total of 60 ASA I-II patients aged between 18 and 65 years who were to undergo distal upper extremity surgery in our clinic between July 2015 and January 2016 were evaluated retrospectively. ASA I: A normal healthy patient(Healthy, non-smoking, no or minimal alcohol use). ASA II: A patient with mild systemic disease (Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity ($30 < \text{BMI} < 40$), well-controlled DM/HTN, mild lung disease). These operations included all of upper extremity surgery such as soft tissue operations, fracture of distal radius or carpal tunnel syndrome, etc. (ClinicalTrials.gov ID: NCT02550782)

Measurements

Patients were divided into two groups according to the analgesic protocol given in the postoperative period.

Group 1: n=30: infraclavicular patient-controlled perineural bupivacaine (0.5 % MARCAIN flacon, Astra Zeneca, Sweden) (0.1 % bupivacaine, bolus dose 5 ml, infusion rate 5 ml/h, lockout time 1 hour)(14).

Group 2: n=30: infraclavicular patient-controlled perineural bupivacaine + dexmedetomidine (PRECEDEX 200 mcg, Abbott, USA) (0.1 % bupivacaine + 200 mic/100 cc dexmedetomidine, bolus dose 5 ml, infusion rate 5 ml/h, lockout time 1 hour)(15).

Infusion dose of dexmedetomidine was adjusted so as not to exceed 1 mic/kg.

Patients in group 1 and group 2 were selected from patients operated on exactly the same anesthetic protocols. Patients who underwent infraclavicular nerve block and infraclavicular perineural catheter insertion prior to surgery and who were given analgesia by the patient-controlled method in the postoperative period were selected. Patients who received bupivacaine and bupivacain + dexmedetomidine infusion via the perineural catheter in the postoperative period were included in the study for the purpose of the study.

In our clinic; after the patients are brought to their services, patient-controlled analgesia was initiated by an anesthetist, when the patient's visual analogue scale ≥ 4 . Time of the first analgesic administered was taken as the Minute 0. All the patients were informed about the patient-controlled analgesia device and told to push button of the device if visual analogue scale ≥ 4 . Patients NIBP, heart rate (HR), SpO₂, modified ramsey scale for the sedation (1-6: 1: agitated, restless; 2: oriented, cooperative; 3: responding to commands only; 4: brisk response to light glabellar tap; 5: sluggish response to light glabellar tap and 6: no response)(16), VAS, first analgesic administration time, amount of analgesic needed by the patients and nausea/vomiting were recorded at the minutes 0, 30, 60, 90 and 120, and then at the hours 4, 6, 8, 12 and 24.

If a patient used 10 ml of the analgesic and has still pain, applied intravenous 100 mg Tramadol HCl. If the patient has still pain after 100 mg of iv tramadol, diclofenac sodium administered intramuscularly.

Infraclavicular perineural catheter was removed by the anesthetist at the end of 24th hour and all the patients with infraclavicular perineural inserted underwent neurological examination of the forearm after 1 month.

Statistical analyses:

The study power was calculated based on the study by Esmoğlu et al.(13) in which dexmedetomidine prolonged the duration of analgesia from an average of 670 (70) to 880 (70) minutes. Considering perineural single dose administration, this SD of 70 minutes was taken as 100 minutes for the perineural infusion our study. Accordingly, study strength value of 85% was obtained at the significance level of $p < 0.0500$ in the two group with sample size of 30 and 30.

One-Sample Kolmogorov-Smirnov Test was used to determine the normal distribution (Table 3). In the intergroup comparisons; Chi-square test was used for the categorical variables (Table 2), Student's t-test for normally distributed continuous variables (Table 1 and Table 3) and Mann-Whitney U-test variance analysis for the non-normally distributed continuous variables and ordered variables (Table 3). Statistical analysis was performed using SPSS 21.0 for Windows package software and $p < 0.05$ values were considered as statistically significant.

Table 1: Mean age of the groups*

| | Group | N*1 | Mean | Std. Deviation**1 | p |
|-------------|-------|-----|-------|-------------------|-------|
| Age (years) | 1 | 30 | 43,40 | 12,615 | 0.456 |
| | 2 | 30 | 45,73 | 11,435 | |

* t Tests , * 1: patient number ** 1: standard deviation

RESULTS

The study included total 60 patients over 18 years old. Mean age of all patients was found as 44.57±11.9 with 27 female and 33 male patients. No significant difference was found between the groups in terms of age and gender, (As shown in Table 1 and Table 2).

When systolic (SAP) and diastolic arterial pressures (DAP) monitored in our study were compared between the groups; SAP was found to be

significantly higher in the Group 1 compared to the Group 2 at 6th hour (p: 0.007). SAP values measured at the hours 8 and 12 were higher in the Group 2, but the difference was not statistically significant (p: 0.920, p: 0.347). Diastolic arterial pressures were higher in the Group 1 in the first two hours and at the hours 24, but the differences were not statistically significant. Whereas, these values were significantly higher in the Group 1 and the 4th and 6th hours (p: 0.000, p: 0.003)(Table 3) (Figure 1).

Table 2: Gender of groups*

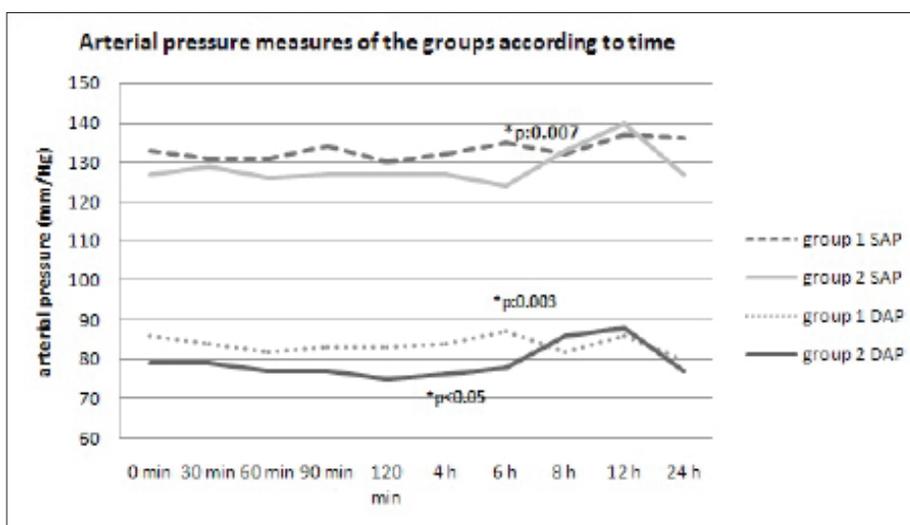
| | | Group 1 | Group 2 | Total | p |
|-------|------------------------|---------|---------|-------|-------|
| | Male (n ²) | 16 | 17 | 33 | |
| | Female(n) | 14 | 13 | 27 | 0.799 |
| Total | | 30 | 30 | 60 | |

*Chi-Square Tests, * 2: number of subject

Table 3: Systolic and diastolic arter pressure and heart rate of the groups according to time

| | Systolic Arter Pressure | | | Diastolic Arter Pressure | | | Heart Rate | | |
|------------|-------------------------|----------------|--------|--------------------------|---------------|--------|--------------|-------------|--------|
| | Group 1 | Group 2 | p | Group 1 | Group 2 | p | Group 1 | Group 2 | p |
| 0.minute | 133,50 ± 16,2 | 127,87 ± 21,0 | .251 | 86,63 ± 11,3 | 79,37± 14,3 | .347 | 69,70 ± 14,8 | 73,73 ± 7,6 | .190 |
| 30.minute | 131,67 ±15,5 | 129,23 ± 17,6 | .574 | 84,77 ±11,1 | 79,90 ± 10,3 | .943 | 70,90 ± 14,8 | 73,90 ± 8,5 | .342 |
| 60.minute | 131,47 ±14,1 | 126,83 ± 18,0 | .273 | 82,53 ± 8,6 | 77,20 ± 11,1 | .388 | 70,70 ± 15,7 | 74,07 ± 7,2 | .290 |
| 90.minute | 134,20 ± 15,5 | 127,20 ± 16,8 | .100 | 83,27 ± 9,6 | 77,30 ±10,2 | .976 | 71,20 ± 15,5 | 74,20 ± 8,0 | .352 |
| 120.minute | 130,63 ± 15,2 | 127,13 ± 16,3 | .395 | 83,07 ± 11,5 | 75,63 ± 8,4 | .302 | 70,63 ± 13,4 | 75,53 ± 6,6 | 0.79 |
| 4. hour* | 132,83 ± 12,7* | 127,20 ± 13,3* | .100 | 84,47± 8,6 * | 76,33 ± 11,5* | .000** | 71,90 ± 9,9 | 76,33 ± 7,0 | 0.51 |
| 6. hour* | 135,63 ± 16,4 | 124,67 ± 13,8 | .007** | 87,83± 13,1* | 78,33± 10,5* | .003** | 73,30 ± 13,7 | 75,70 ± 6,7 | .395 |
| 8. hour | 132,67 ± 13,1 | 133,00 ± 12,6 | .920 | 82,50 ± 8,9 | 83,00 ± 9,1 | .832 | 72,17 ± 12,3 | 80,27 ± 8,2 | .004** |
| 12. hour* | 137,00 ± 14,1 | 140,67 ± 15,7 | .347 | 86,67 ± 13,0* | 88,67 ± 10,4* | .674 | 74,47 ± 12,5 | 83,40 ± 8,0 | .002** |
| 24. hour* | 128,00 ± 14,7* | 124,67 ± 15,4* | .329 | 80,00 ± 10,1* | 77,33 ± 8,2* | .301 | 70,47 ± 10,7 | 77,07 ± 8,0 | .002** |

*mann whitney u test, ** p<0.05 values were considered as statistically significant. Student’s t-test for normally distributed continuous variables and Mann-Whitney U-test variance analysis for the non-normally distributed continuous variables and ordered variables.



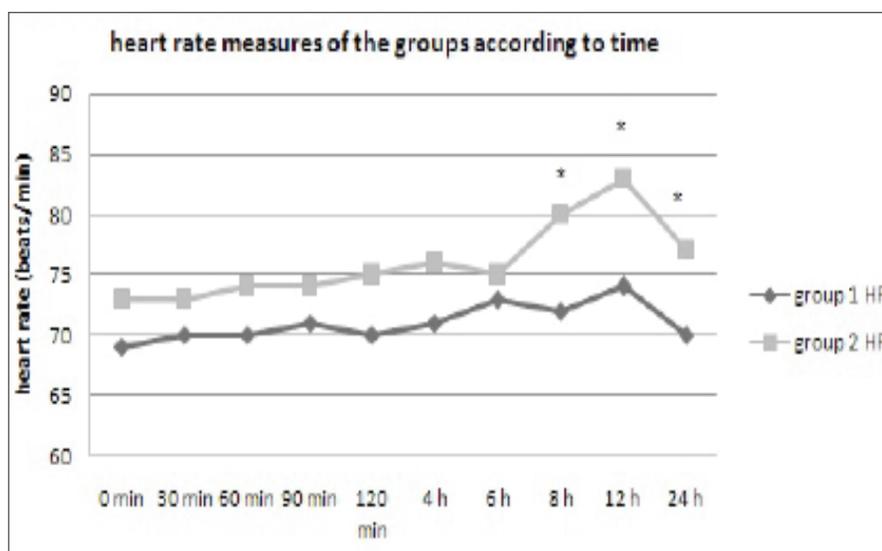
Systolic (SAP) arterial pressures was found to be significantly higher in the Group 1 at 6th hour. Diastolic (DAP) arterial pressures were higher in the Group 1 at 4th and 6th hours.

Figure 1: Arterial pressure measures of the groups according to time

When heart rates were compared between the groups; heart rates were higher in the Group 2 at all hours. However, these results were found to be statistically significant at the hours 8, 12 and 24 (p: 0.004, p: 0.002, p: 0.002) (Table 3) (Fig. 2).

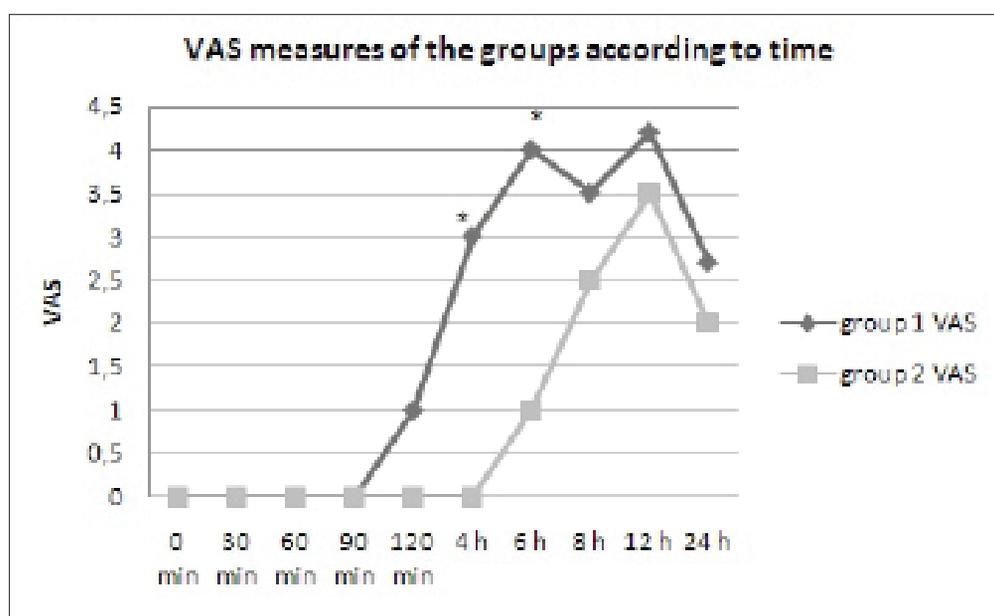
In none of our patients SpO2 dropped under 95% and sedation was not observed in any patient in the dexmedetomidine group.

When VAS values were compared between the groups in our study; patients in the Group 1 were found to significantly feel pain and require analgesics at the 4th and 6th hours (p: 0.002, p< 0.05). Whereas time of the first sensation of pain in the Group 2 was found as the 6th hour. There was pain sensation in both the groups at the hours 8, 12 and 24, but the difference were not statistically significant (p: 0.592, p: 0.136, p: 0.195; respectively) (Fig. 3).



*Heart Rates (HR) were higher in the Group 2 at all hours. However, these results were found to be statistically significant at the hours 8, 12 and 24 (p: 0.004, p: 0.002, p: 0.002)

Figure 2: Heart rate measures of the groups according to time.



*patients in the Group 1 were found to significantly feel pain and require analgesics at the 4th and 6th hours (p: 0.002, p< 0.05)

Figure 3: VAS measures of the groups according to time

When the number of patient initiated requests for analgesia was examined; the mean numbers of the need for analgesia was found as 5.8 ± 1.4 times in the Group 1 and 2.2 ± 0.4 times in the Group 2 ($p < 0.05$).

Nausea/vomiting occurred in 2 patients in the Group 1 and 3 patients in the Group 2. No any problem was found in neurological examinations of our patients, that were performed after 1 month.

DISCUSSION

We found that dexmedetomidine added to bupivacaine infused through an infraclavicular catheter prolonged the time until analgesia was requested, and decreased the need for 24-hour analgesia without significant systemic side effects (sedation, bradycardia and hypotension etc.) at these doses.

Dexmedetomidine is an alpha-2 agonist affecting the central nerve system. It has several effects such as decrease in blood pressure, sedation, sleep, analgesia and shivering. In our study, systolic and diastolic arterial pressures were lower in the group which received dexmedetomidine added to bupivacaine compared to the group administered bupivacaine alone. These lower values were attributed to the inhibition of sympathetic activity with the postsynaptic activation of alpha 2 adrenoceptor in central nervous system, resulting in decreased heart rate and blood pressure(17,18). In our study, contrary to expectations heart rate was in rise in the Group 2 than in the Group 1 over 24 hours. This condition monitored from the 0th minute was attributed to the personal characteristics of patients and dose of dexmedetomidine kept low. Both arterial pressures and heart rates increased at the 8th and 12nd hours were attributed to the again high VAS values at the same hours.

It has been demonstrated in many studies that, dexmedetomidine increases the duration of postoperative analgesia and prolongs time of the first need for analgesia(8,13,19-23). Similarly, in our study also dexmedetomidine was found to increase the duration of postoperative analgesia and prolong time of the first need for analgesia. Time for the first need for analgesia was found as the 4th hour in bupivacaine and 6th hour in dexmedetomidine group. Also total need for analgesics were significantly reduced in the Group 2. Masuki et al. reported that, dexmedetomidine causes reduction of local anesthetic absorption and thus prolongs its effect by inducing vasoconstriction around the injection(24). Likewise in a study by Memiş(25) and Esmaoğlu(13), the authors attributed this prolongation effect to reduction of the release of norepinephrine by peripheral alpha 2 agonists, resulting in a decrease in pain because of the independent inhibitor effects on action potential of the nerve fibers.

Swami et al. stated that administration of perineural dexmedetomidine has a sedative effect(15). Guo et al. noted that the the sedative effect results from the suppression of the release of substance P matter which plays a role in the pain conduction at the dorsal root level and the activation of alpha-2 in the locus cereleus(18). Differently in their study Bekker et al. concluded that perineural administration of dexmedetomidine may be helpful in the case of sedation(26). In parallel, in our study perineural infusion of dexmedetomidine did not cause sedation in any of our patients. This finding may be because

the infusion of dexmedetomidine in this study results in a more peripheral than central alpha 2 effect(27).

None of or patients developed neurological deficits. This is parallel to the animal studies by Brummet in which dexmedetomidine did not caused axon or myelin damage even in high doses (25-40 mic/kg) (12).

Good postoperative analgesia helps patients to return their normal daily lives in a shorter time, increases patient satisfaction and reduced the length of stay in hospital and costs. Regional anesthesia techniques provide a excellent pain control, contributing to these processes. In recent years, peripheral nerve blocks and even peripheral nerve catheter insertion have been introduced in order to protect patients against the side effects of opioids used for postoperative purposes(28,29). However, peripheral nerve catheter is a procedure which takes longer time and is more expensive and painful for patients with a higher rate of complications and needs more postoperative care(28,29). Ultrasound guidance reduces the time necessary for catheter insertion, and may improve success rates(30). Patients who underwent ultrasonography were included in this study and the success rate of the blocks and the insertion of catheters are 100%. There are no technical failures of PCA devices.

Our study has some limitations. First, number of the intragroup patients are small. Further studies with larger number of cases are needed in order to obtaine stronger data. Second, plasma levels of dexmedetomidine that could support its peripheral rather than central effects were not studied. Third, because of feared perineural side effects of dexmedetomidine, lock-out time was defined as 1 hour. This condition may be caused by the ineffectiveness of bupivacaine alone. Fourth, VAS values was evaluated at rest, not at movement.

CONCLUSION

We found that dexmedetomidine added to bupivacaine infused through an infraclavicular catheter prolonged the time until analgesia was requested, and decreased the need for 24-hour analgesia without any side effect (sedation, bradycardia and hypotension etc.) at these doses. Patient-controlled administration of dexmedetomidine at low doses provides a comfortable and good postoperative analgesia, high patient satisfaction and low incidence of adverse effects.

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