

## CLINICAL SCIENCE

# Regional intravenous anesthesia in knee arthroscopy

Mahmut Arslan,<sup>1,II</sup> Mehmet Cantürk,<sup>1,II</sup> Dilşen Örnek,<sup>1,II</sup> Mehmet Gamlı,<sup>1,II</sup> Yaşar Pala,<sup>1,II</sup> Bayazıt Dikmen,<sup>1,II</sup> Melekşah Basaran<sup>1,II</sup>

<sup>1</sup>Ministry of Health, Ankara Numune Training and Research Hospital, Ankara, Turkey. <sup>II</sup>Anesthesiology and Reanimation Department, Ankara, Turkey.

**OBJECTIVE:** The goal of the study was to investigate the regional intravenous anesthesia procedure in knee arthroscopy and to evaluate the effects of adding ketamine over the anesthesia block character and tourniquet pain.

**MATERIAL/METHOD:** Forty American Society of Anesthesiologists (ASA) II patients who received knee arthroscopy were enrolled. After monitoring, a peripheral IV line was inserted. The venous blood in the lower extremity was evacuated with a bandage, and the proximal cuff of the double-cuff tourniquet was inflated. The patients were randomly split into two groups. While Group P received 80 ml 0.5% prilocaine, Group PK received 0.15 mg/kg ketamine (80 ml in total) via the dorsum of the foot. We recorded onset time of the sensory block, end time of the sensory block, presence of the motor block, the time when the patient verbally reported tourniquet pain and surgical pain, duration of tourniquet tolerance, fentanyl consumption during the operation, time to first analgesic requirement, methemoglobin values at 60 minutes, operative conditions, 24-hour analgesic consumption, discharge time, and hemodynamic parameters.

**RESULTS:** The body mass index (BMI) of the patients who required general anesthesia was significantly higher than the BMI of other patients. The onset time of the sensory block was shorter for those in Group PK, but the time to first analgesic requirement was longer.

**CONCLUSION:** Regional intravenous anesthesia using the doses and volumes commonly used in knee arthroscopy may be an inadequate block among patients with high BMI values. Moreover, the addition of ketamine to the local anesthetic solution may produce a partial solution by shortening the onset of sensory block and prolonging the time until the first analgesic is required.

**KEYWORDS:** Regional Intravenous Anesthesia; RIVA; Arthroscopy; Prilocaine; Analgesia; Motor block.

Arslan M, Cantürk M, Örnek D, Gamlı M, Pala Y, Dikmen B, Basaran M. Regional intravenous anesthesia in knee arthroscopy. Clinics. 2010;65(9):831-835.

Received for publication for April 8, 2010; First review completed on May 17, 2010; Accepted for publication on May 18, 2010

E-mail: dilsenpinar@yahoo.com

Tel.: 05057373828

## INTRODUCTION

Regional intravenous anesthesia (RIVA) was first described by Bier in 1908 and gained popularity following modifications made by Holmes in 1963.<sup>1</sup> The most important advantages of using the technique are that it's easy-to-apply, reliable, and cost-effective.<sup>2</sup> It has gained wide popularity in upper extremity surgery due to its reported success rates of between 94-98%.

Knee arthroscopy is one of the most commonly performed orthopedic procedures. Various anesthesia methods have been successfully used in this procedure, such as local anesthesia, peripheral-neuroaxial blocks, and general anesthesia. Nonetheless, experts continue to debate which anesthesia method would increase patient satisfaction, best fit surgical conditions, and allow the most effective usage of the operating room.<sup>4,5</sup>

Although RIVA has been used in many surgeries involving the lower extremities, except for one case report, there has been no study of using it in knee arthroscopy.<sup>6</sup>

In the current study, we aimed to determine whether RIVA could be effective in knee arthroscopy and to evaluate the effects of adding ketamine to the regimen over block character and tourniquet pain.

## MATERIALS AND METHODS

Following the approval of the Ministry of Health Ankara Numune Training and Research Hospital ethics committee, 40 patients (19-65 years old) with ASA 1-2 physical status who signed an informed consent form were included in the current study. Patients with the following conditions were excluded from the study: Reynaud disease; sickle cell anemia; peripheral neuropathy or central nervous system disorder; deep vein thrombosis, infection, skin problems, or active arthritis in the related extremity; uncontrolled hypertension; and presence or history of allergic reaction to prilocaine or ketamine. The patients who required general anesthesia due to tourniquet pain or surgical pain were recorded and also excluded from the study.

After the patients were inside the operating room, we measured their heart rate, noninvasive blood pressure, and respiratory rate. Their O<sub>2</sub> saturation was analyzed using pulse oximetry, and the ECG (PM 8060 Vitara, Germany) was examined. Following the insertion of a peripheral IV line in the dorsum of the foot, all the patients were premedicated with intravenous 0.04 mg/kg midazolam. Then we placed a double-cuff tourniquet (8) (VBM, Medizintechnik GmbH 30 inch/76 cm) above knee. The patients were randomly split into two groups. Group P received 0.5% prilocaine (80 mL), and Group PK received 0.5% prilocaine + 0.15 mg/kg ketamine (80 mL in total).

The prepared solutions were delivered from the dorsum of the foot in 90 seconds. A sensory block was started and was evaluated five minutes following the drug delivery, and the examination was repeated once a minute using a pinprick test. The patient was instructed to move his or her big toe at one-minute intervals to assess the motor block.

*Onset time of sensory block* was defined as the time that passed until the development of a sensory block in all the dermatome levels tourniquet.

*End time of sensory block:* Development of sensory block after the release of the tourniquet was evaluated each minute using the pinprick method.

*Motor block evaluation:* Failure to flex the big toe indicated the presence of a motor block.

*Assessment of the tourniquet pain* was done using VAS (verbal pain scale) at 0, 10, 20, 30, 40, 50, and 60 minutes, beginning with the inflation of the distal cuff (Table 1).

*Surgical pain* was evaluated following the incision by VAS at 0, 10, 20, 30, 40, 50, and 60 minutes.

*Duration of tourniquet tolerance* was the length of time between distal cuff inflation and time when patient asked for analgesic.

*Perioperative analgesic consumption:* As additional analgesic was needed due to tourniquet pain or surgical pain, 50 µg fentanyl iv bolus delivery was performed (maximum 3 µg/kg). The amounts consumed for tourniquet pain and surgical pain were recorded separately.

*Perioperative period:* Average arterial pressure, heart rate, and SpO<sub>2</sub> were recorded before and after the tourniquet placement, at the moment when the distal cuff was inflated and when the proximal cuff was deflated, during the surgical incision and first 30 minutes at 5-minute intervals following the incision, and at 15-minute intervals during the ensuing period.

*Postoperative period:* One and five minutes following the release of the tourniquets, values for heart rate, blood pressure, and SpO<sub>2</sub> were recorded.

The interval between the inflation and deflation of the first tourniquet was recorded as the tourniquet duration. The interval between the tourniquets' deflation and time to first analgesic requirement was recorded as the time to first analgesic requirement. As needed, patients were delivered a

**Table 1 - Verbal rating scale.**

SCORE	Pain expression
1	No pain
2	Mild pain
3	Moderate pain
4	Severe pain
5	Very severe pain

75 mg oral diclofenac tablet as an analgesic, and the analgesic consumption within the first 24 hours was noted.

*Operative conditions* were graded by the surgeon after the end of the operation as 0: unsuccessful, 1: poor, 2: acceptable, and 3: perfect.

The patients were evaluated in terms of numbness of the tongue or around the mouth, dizziness, tinnitus, drowsiness, tremor, convulsions, and toxicity signs, such as arrhythmia and cyanosis, as well as psychomimetic side effects associated with ketamine, such as hypertension, tachycardia, euphoria, hallucinations, confusion, and delirium. Sixty minutes after the end of the operation, we measured methemoglobin levels of the patients.

**Statistical Analysis**

The data were analyzed using the SPSS 12 software program. We investigated the distribution of variables (normal or not) obtained on the basis of equal intervals and ratio scale. The Kolmogorov-Smirnov concordance test and the low number of subjects alongside an examination of the histograms by calculating the kurtosis and skewness indicated that the distribution was not normal. The analysis was conducted using the chi-square test of categorical data and the Mann-Whitney U test of the variables with abnormal distribution that were collected on the basis of the ratio. P<0.05 was recognized as statistically significant.

**RESULTS**

There was no statistically significant difference between the groups with regard to age, weight, gender, ASA physical status scores, operation length, and tourniquet duration (Table 2).

We had to switch to general anesthesia for 5 patients in Group P and 6 patients in group PK.

The onset time for using the sensory block was significantly shorter in the PK group. There was no statistically significant difference between the groups in terms of the end time of sensory block usage, motor block percentages, and duration of tourniquet tolerance (Table 3).

**Table 2 - Demographic data, tourniquet duration, and operation length (median value, minimum-maximum).**

	P	PK	P value
Age (year)	45 (19-65)	42.5 (19-58)	0.291
Weight (kg)	80 (58-87)	76.5 (57-95)	0.870
Height (cm)	165,5(155-185)	170 (152-185)	0.472
Gender F/M	9/11	8/12	0.749
ASA I/II	5/15	11/9	0.078
Tourniquet duration (min.)	50 (45-69)	49 (14-83)	0.646
Operation llength (min.)	32 (21-48)	35 (19-69)	0.694

**Table 3 - Onset time of sensory block (OTSB), end time of sensory block (ETSB), presence of motor block (MB), duration of tourniquet tolerance (DTT) (median value, minimum-maximum).**

	GROUP P	GROUP PK	P value
OTSB (min.)	14 (9-19)	10.50 (7-18)	0.047
ETSB (min.)	8 (5-18)	10 (5-15)	0.323
MB	20%	21.4%	<0.999
DTT (min.)	18 (2-55)	25 (6-41)	0.793

**Table 4 - VAS values for tourniquet pain (TPVAS) (median, minimum-maximum).**

	GROUP P	GROUP PK	P value
TPVAS0	2 (1-4)	1 (1-3)	0.036
TPVAS10	2 (1-4)	1,5 (1-4)	0.175
TPVAS20	2 (1-4)	3 (1-4)	0.385
TPVAS30	2 (1-4)	2,5 (1-4)	0.698
TAVAS40	3 (1-4)	3 (1-4)	0.885
TAVAS50	3,5 (2-4)	4 (2-5)	0.536

**Table 5 - Surgical pain VAS values (SPVAS) (median, minimum-maximum).**

	GROUP P	GROUP PK	P value
SPVAS0	1 (1-3)	1 (1-3)	0.620
SPVAS10	2 (1-2)	1 (1-1)	0.041
SPVAS20	1 (1-4)	1 (1-2)	0.354
SPVAS30	2 (1-4)	1 (1-1)	0.044

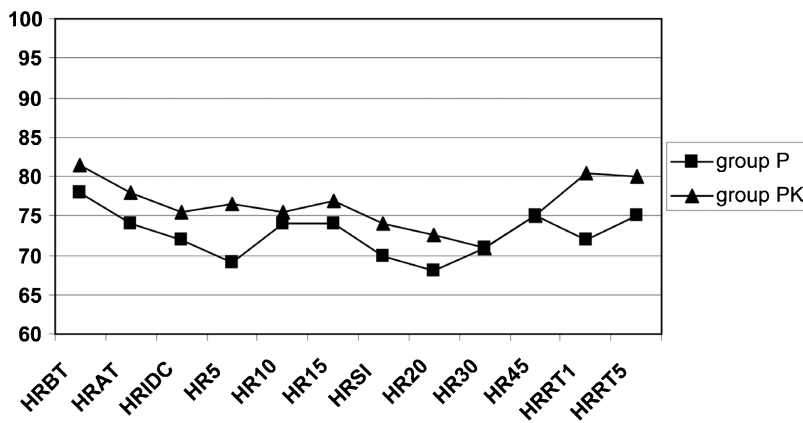
**Table 6 - Fentanyl consumption for tourniquet pain (FCTP), fentanyl consumption for surgical pain (FCSP), and operative conditions (OC) (median value, minimum-maximum).**

	GROUP P	GROUP PK	P value
TAFT(µg)	150(0-250)	100(0-200)	0.859
CAFT(µg)	0(0-50)	0(0-250)	0.354
OK	2(1-3)	3(2-3)	0.080

The tourniquet pain value at 0 minutes was significantly high in the P group (Table 4). VAS values for surgical pain were significantly high at 10 and 30 minutes (Table 5).

Between the groups, there was no significant difference with regard to fentanyl consumption for tourniquet pain, fentanyl consumption for surgical pain, and operative conditions (Table 6).

While time to first analgesic requirement was significantly longer in the Group PK, there was no significant difference between the groups in terms of 24-hour analgesic consumption (Table 7). No significant difference was determined with regard to discharge time and methemoglobin values at 60 minutes (Table 8).



**Figure 1 - Variation of heart rates relative to time.**

HRBT: Heart Rate Before tourniquet, HRAT: After tourniquet, HRIDC: Inflation of the distal cuff, HRSI: Surgical incision, HRRT1: First minute after the release of the tourniquet, HRRT5: Fifth minute after the release of the tourniquet

**Table 7 - Time to first analgesic requirement, 24-hour analgesic consumption (median value, minimum-maximum).**

	GROUP P	GROUP PK	P value
İAGZ(dk)	177.5(97-577)	468.50(192-1028)	0.002
24 AT(mg)	150(0-150)	75(75-150)	0.298

**Table 8 - Discharge time (DS) and methomoglobin values at 60 minutes (metHb) (median value, minimum-maximum).**

	GROUP P	GROUP PK	P value
MetHb(%)	3.1(1.1-6.1)	3.95(2.7-7.8)	0.101
DS(hour)	23(20-25)	23.5(20-26)	0.841

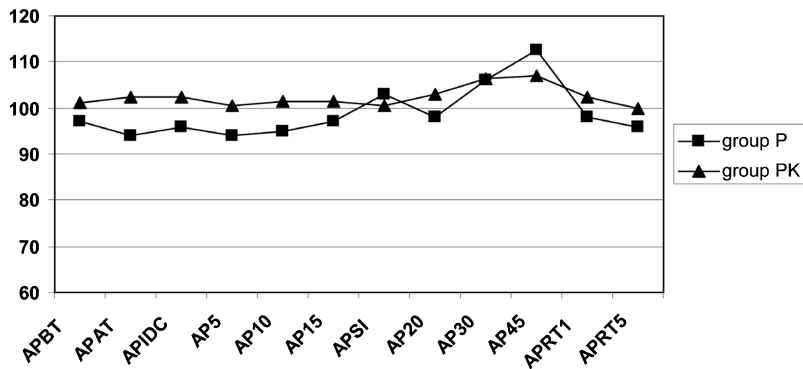
There was no significant difference between the groups in terms of the heart rate (HR) (Figure 1), mean arterial pressure (Figure 4), and oxygen saturation.

After the release of the tourniquet, we observed perioral numbness in 4 patients in Group P and 3 patients in Group PK, tinnitus in one patient in each group, euphoria in one patient in Group PK, tremor in 3 patients in Group PK and one patient in Group P, and dizziness in 3 patients in Group PK. Side effects required no intervention. There were no differences between the groups in terms of side effects.

**DISCUSSION**

In the current study, onset time of sensory block was shorter (10.5 minutes – 14 minutes,  $p=0.047$ ), tourniquet pain at 0 minutes (baseline) and surgical pain at 10 and 30 minutes were lower, and time to first analgesic requirement was longer (177.5 minutes – 468.5 minutes,  $p=0.002$ ) in Group PK. Six patients (30%) in group PK required a switch to general anesthesia.

There are few studies in the literature on using the RIVA procedure in lower-extremity surgery. Lehman and Jones applied the RIVA method to 54 patients for procedures involving the knee and its distal parts by delivering 3.3 mg/kg 0.25% lidocaine<sup>7</sup> and switched to another method for cases in which patients failed to achieve anesthesia within 15 minutes. Their success rate with this method was 94%. Davies applied RIVA by delivering 3 mg/kg 0.5%



**Figure 2** - Variation of average blood pressures relative to time.

APBT: Average blood pressure Before tourniquet, APAT: After tourniquet, APIDC: Inflation of the distal cuff, APSI: Surgical incision, APRT1: First minute after the release of the tourniquet, APRT5: Fifth minute after the release of the tourniquet.

prilocaine to 48 patients undergoing foot surgery; he achieved adequate analgesia in 44 patients and sedation in 1 patient, and additional local anesthetic infiltration was required in 3 patients.<sup>8</sup> Nusbaum and Hamelberg performed RIVA by using calf tourniquets and delivering 30-40 ml 0.5% lidocaine to 40 patients undergoing foot and ankle surgery and achieved a successful block in 39 patients.<sup>9</sup> Kim et al. placed a tourniquet at the ankle level, used 35 mL 0.33% or 0.5% lidocaine, and succeeded with 31 (79.5%) of 39 patients.<sup>10</sup> Schurg et al. used 200 mg prilocaine during foot surgery on 17 patients, administered an additional 100 mg prilocaine when adequate analgesia was not achieved within 5 minutes, and succeeded with 15 patients.<sup>11</sup> Our success rate of 72.5% was similar to that experienced by Kim et al.

In the present study, we had to switch to general anesthesia in 5 (25%) patients in Group P and 6 (30%) patients in Group PK. The underlying causes for the switch to general anesthesia in Group P were unsuccessful block in 2 patients, incisional pain in one patient, and tourniquet pain in one patient. Among the patients in Group PK, we switched to general anesthesia due to tourniquet pain in 5 patients and incisional pain in 1 patient. The BMIs of patients who were switched to general anesthesia were significantly higher than others (median values: 29.3 – 25.1,  $p = 0,035$ ). We believe that this difference reduces the success rate of the block because it enlarges the area that will receive the solution and makes complete evacuation of the extremity difficult by complicating the application of the Esmarch bandage. The underlying reason for switching to general anesthesia was tourniquet pain in 7 (63%) of 11 patients. We believe that the high number of muscles in the femoral region and the various positions assumed by the knee during arthroscopy may increase the tourniquet pain. Lehman and Jones used a femoral tourniquet in their studies and gained a higher success rate than we did. Their patients who were subjected to RIVA presented with minor orthopedic complaints, such as closed reduction, debridement, foreign body removal, and tendon repair. Nonetheless, the anesthetic volume they used was higher. We think the difference in the success rates may be due to those two reasons.

In light of their 20-year experience, Brown et al. stated that the injection of 150 mL local anesthetic solution should be required in RIVA with femoral tourniquet.<sup>4</sup> Al-Metwalli and Mowafi applied RIVA successfully with 40 mL 0.5%

lidocaine by using the “modified inter-cuff” technique that they described in a case report they published in 2002.<sup>6</sup> We took those two studies into consideration and decided to use an 80 mL solution, following the technique of Al-Metwalli and Mowafi. Our results suggest that while applying RIVA with a femoral tourniquet, the volume to be used should be determined according to the BMIs of the patients.

In the present study, among the ketamine group, onset time of sensory block was significantly shorter and the time to the first analgesic requirement was longer. Moreover, tourniquet pain at 0 minutes as well as surgical pain at 10 and 30 minutes were significantly lower in the ketamine group. While only 2 patients in the ketamine group required additional analgesic due to pain in the surgical area (100 µg fentanyl in total), 4 patients in the other group required additional anesthetic (450 µg fentanyl in total).

The local anesthetic effect of ketamine was first shown by Dowdy et al. who experimented on laboratory animals in 1973.<sup>12</sup> Following this result, Amiot et al. applied RIVA during upper-extremity surgery and delivered a 40 mL 0.5% ketamine solution to 14 patients, and they succeeded in establishing complete sensory block within an average time of 14 minutes.<sup>13</sup> While the operation was completed with this technique in 12 patients, the average time for complete motor block was 17.3 minutes in 9 patients, and 4 patients received 5 mg iv diazepam due to failure to tolerate a tourniquet. Following the release of the tourniquet, all the patients demonstrated unconsciousness for 10 minutes, but no sequelae ensued. Durrani et al. administered 0.6 mL/kg ketamine in 0.5%, 0.3%, and 0.2% concentrations along with RIVA in order to investigate whether ketamine could provide adequate surgical anesthesia without inducing unconsciousness following the release of the tourniquet.<sup>14</sup> While 0.2% of the group was excluded from the study because of unbearable tourniquet pain, they succeeded in establishing complete sympathetic, sensory, and motor block in the other two groups. Even after the release of the tourniquet, hemodynamic signs showed no marked difference. All the volunteers demonstrated loss of sense of reality and/or hallucinations, but none of them exhibited loss of consciousness. Although normal orientation was achieved in all the volunteers within 20 minutes by administering intravenous diazepam, patients defined this experience as unacceptable and unpleasant.

Researchers who completed anatomical studies reported the presence of NMDA receptors in unmyelinated sensory



axons.<sup>15</sup> The blockage of those receptors may be responsible for the peripheral analgesic effect of ketamine. Frenkel and Urban showed that ketamine blocked human Na<sup>+</sup> channels when delivered at higher concentrations than in general anesthesia.<sup>16</sup> This result was consistent with the findings of Durrani et al. Tverovsky et al. reported that ketamine increased the anesthetic and analgesic effects of bupivacaine in infiltration anesthesia through a peripheral mechanism.<sup>17</sup> Since we cannot expect achieving a local anesthesia with a 0.15 mg/kg direct dose of ketamine, we believe that the positive effects obtained in our study were associated with the interaction of ketamine and prilocaine as reported in the studies of Tverovsky et al. Gorgias et al. conducted the only study in which local anesthetic and ketamine were delivered together and reported that the addition of 0.1 mg/kg ketamine to the lidocaine delayed the tourniquet pain and reduced the analgesic consumption for tourniquet pain.

Because there was no data on the onset time of the sensory block and time to the first analgesic requirement, we cannot compare the results with those of our study. One of the most important reasons that doctors rarely use RIVA is that side effects may arise because it requires a high-dose of local anesthetic. The most feared side effect of that local anesthetic is methemoglobinemia. Prilocaine metabolites, 2-hydroxy, 2-methylaniline, and 2-methylaniline, oxidize normal hemoglobin and lead to methemoglobinemia. If a patient experiences clinical cyanosis and is unresponsive to 100% oxygen therapy, the healthcare professional should suspect methemoglobinemia. In healthy individuals, clinical symptoms such as dyspnea, nausea, and tachycardia occur when the methemoglobin level rises above 30%. When the methemoglobin level reaches 55%, consciousness is affected, whereas a level of 70% is generally fatal. Some authors stated that no treatment should be applied if methemoglobin levels are below 30% among patients with no cardiopulmonary problems.<sup>18</sup> In the current study, we used 400 mg prilocaine for anesthesia in arthroscopic surgery.

In their study comparing the use of lidocaine and prilocaine for RIVA, Bader et al. determined that the highest methemoglobin levels occurred 60 minutes after the release of the tourniquet. Therefore, we evaluated methemoglobin levels at 60 minutes. The highest methemoglobin level we determined was 7.8%. None of the patients in our study displayed cyanosis or dyspnea. We observed perioral numbness in 3 patients and tinnitus in 2 patients. Thus, we believe that the dose and volume we used in the current study are safe.

Using the RIVA procedure for knee arthroscopy with the dose and volumes used in the current study may not

achieve an adequate block, particularly in patients with high BMIs. We believe that determining the volume and doses required for the RIVA method, particularly in surgical procedures where a femoral tourniquet is needed in the lower extremity, will elevate the success rate. Nonetheless, the addition of ketamine to the local anesthetic solution may partially contribute to the block quality by shortening the onset of the sensory block and delaying the time when the first analgesic is required.

## REFERENCES

- Hilgenhurst G. The Bier block after 80 years: a historical review. *Reg Anesthesia*. 1990;15:2-5.
- Chilvers CR, Kinahan A, Vaghadia H, Merrick PM. Pharmacoeconomics of intravenous regional anaesthesia vs general anaesthesia for outpatient hand surgery. *Can J Anaesth*. 1997;44:1152-6.
- Henderson CL, Warriner CB, McEwen JA, Merrick PM. A North American survey of intravenous regional anesthesia. *Anesth Analg*. 1997;85:858-63, doi: 10.1097/0000539-199710000-00027.
- Brown EM, McGriff JT, Malinowski RW. Intravenous regional anaesthesia (Bier block): review of 20 years' experience. *Can J Anaesth*. 1989;36:307-10.
- Horlocker TT, Hebl JR. Anesthesia for outpatient knee arthroscopy: is there an optimal technique? *Reg Anesth Pain Med*. 2003;28:58-63.
- Al-Metwalli R, Mowafi HA. A modification of the inter-cuff technique of IVRA for use in knee arthroscopy. *Can J Anaesth*. 2002;49:687-9.
- Lehman WL, Jones WW. Intravenous lidocaine for anesthesia in the lower extremity. A prospective study. *J. Bone Joint Surg*. 1984;66-A:1056.
- Davies JAH. Intravenous regional analgesia with prilocaine for foot surgery. *Anaesthesia*. 1989;44:902-6, doi: 10.1111/j.1365-2044.1989.tb09144.x.
- Nusbaum LM, Hamelberg W. Intravenous Regional Anesthesia for Surgery on the Foot and Ankle. *Anesthesiology*. 1986;64:91-2, doi: 10.1097/0000542-198610000-00014.
- Kim DD, Shuman C, Sadr B. Intravenous Regional Anesthesia for outpatient foot and ankle surgery. *Orthopedics*. 1993;16:1109-13.
- Schurg R, Biscopring J, Bachmann MB, Hempelmann G. Intravenous regional anesthesia of the foot using prilocaine. Clinical aspects, pharmacokinetic and pharmacodynamic studies. *Reg Anaesth*. 1990;13:118-21.
- Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *BJA*. 1996;77:441-4.
- Amiot JF, Bouju P, Palacci JH, Balliner E. Intravenous regional anaesthesia with ketamine. *Anaesthesia*. 1985;40:899-901, doi: 10.1111/j.1365-2044.1985.tb11056.x.
- Durrani Z, Winnie AP, Zsigmond EK, Burnett ML. Ketamine for Intravenous Regional Anesthesia. *Anesth Analg*. 1989;68:328-32, doi: 10.1213/0000539-198903000-00026.
- Carlton SM, Hargett GL, Coggeshall RE. Localization and activation of glutamate receptors in unmyelinated axons of rat glabrous skin. *Neurosci Lett*. 1995;197:25-8, doi: 10.1016/0304-3940(95)11889-5.
- Frenkel C, Urban BW. Molecular actions of racemic ketamine on human CNS sodium channels. *British Journal of Anaesthesia*. 1992;69:292-7, doi: 10.1093/bja/69.3.292.
- Hall AH, Kulig KW, Rumack BH. Drug- and chemical- induced methaemoglobinaemia. Clinical features and management. *Med Toxicol*. 1986;1:253-60.
- Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia. Treatment issues. *Drug Saf*. 1996;14:394-405, doi: 10.2165/00002018-199614060-00005.