Subcutaneous ketamine for postoperative pain relief in Rwanda: a randomized clinical trial

Kétamine sous-cutanée pour soulager la douleur postopératoire au Rwanda : une étude clinique randomisée

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Abstract

Purpose Postoperative pain control is often inadequate in low-income countries such as Rwanda, prompting the search for an inexpensive improvement. A randomized controlled trial was conducted to study the use of subcutaneous ketamine for the management of postoperative pain in patients undergoing major surgery in Kigali, Rwanda.

Methods Fifty-nine patients undergoing major abdominal, head and neck, plastic, or gynecological surgeries were studied. In addition to standard care, patients received five subcutaneous injections of ketamine $1 \text{ mg} \cdot \text{kg}^{-1}$ (ketamine group, $n = 30$) or normal saline (placebo group, $n = 29$) during the postoperative period. The first injection was administered in the postanesthesia care unit and then every 12 hr thereafter starting at 20:00 on the day of surgery. Pain was assessed three times per day using an 11-point verbal response scale. Patients were also assessed for side effects, including nausea and vomiting, hallucinations, nightmares, sedation, hypertension, and seizures.

Results The mean (SD) overall postoperative pain scale score was higher in the control group than in the ketamine

group [4.8 (1.7) vs 3.7 (1.5), respectively; difference of means, 1.1; 95% confidence interval [CI], 0.3 to 1.9; $P = 0.009$]. Brief hallucinations (ketamine group, 11 patients; placebo group, 0 patients; risk difference, 0.37; 95% CI, 0.18 to 0.54; $P < 0.001$) were associated with ketamine administration.

Conclusions Results of this study in Kigali, Rwanda showed that subcutaneous administration of ketamine $1 \text{ mg} \cdot \text{kg}^{-1}$ twice daily, in addition to standard postoperative care, produced a small improvement in postoperative pain but resulted in more minor side effects

Trial registration www.clinicaltrials.gov (NCT02514122). Registered 31 July 2015.

Résumé

Objectif Le contrôle de la douleur postopératoire est souvent inadéquat dans les pays à faible revenu tels que le Rwanda, ce qui suscite la recherche d'améliorations peu onéreuses. Une étude randomisée contrôlée a été réalisée afin d'examiner l'utilisation de kétamine sous-cutanée pour la prise en charge de la douleur postopératoire chez les patients subissant une chirurgie majeure à Kigali, au Rwanda.

Méthode Cinquante-neuf patients subissant une chirurgie abdominale, de la tête et du cou, plastique ou gynécologique majeure, ont participé à l'étude. Outre les soins standard, les patients ont reçu cinq injections sous-cutanées de $1 \text{ mg} \cdot \text{kg}^{-1}$ de kétamine (groupe kétamine, $n = 30$) ou de solution physiologique salée (groupe placebo, $n = 29$) en période postopératoire. La première injection a été administrée en salle de réveil, puis les autres ont suivi toutes les 12 h à partir de 20 h le soir de la chirurgie. La douleur a été évaluée trois fois par jour à l'aide d'une échelle de réponse verbale à 11 points. Les effets

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secondaires, notamment les nausées et vomissements, les hallucinations, les cauchemars, la sédation, l'hypertension et les convulsions, ont également été évalués chez les patients.

Résultats Le score global médian (ÉT) de douleur postopératoire était plus élevé dans le groupe témoin que dans le groupe kétamine [4,8 (1,7) vs 3,7 (1,5), respectivement; différence de moyennes, 1,1; intervalle de confiance [IC] 95 %, 0,3 à 1,9; $P = 0,009$]. De brèves hallucinations (groupe kétamine, 11 patients; groupe placebo, 0 patient; différence de risque, 0,37; IC 95 %, 0,18 à 0,54; $P < 0,001$) ont été associées à l'administration de kétamine.

Conclusion Les résultats de cette étude à Kigali, au Rwanda, montrent que l'administration sous-cutanée de 1 mg·kg⁻¹ de kétamine deux fois par jour, en ajout aux soins postopératoires standard, a entraîné une petite amélioration en matière de contrôle de la douleur postopératoire mais a provoqué davantage d'effets secondaires mineurs.

Enregistrement de l'étude www.clinicaltrials.gov (NCT02514122). Enregistrée le 31 juillet 2015.

Provision of adequate pain relief after surgery is an ethical responsibility of healthcare providers and a fundamental right of every patient.¹ In high-income countries (HICs), good postoperative pain control is a normal part of surgery. This does not appear to be the case in low-income countries (LICs),^A although the magnitude of the problem is uncertain.^{2,3} An observational study of postoperative pain control (manuscript in preparation) conducted by our group in the University Teaching Hospital Kigali (UTHK) suggests poor attention to postoperative pain. Of the first 100 patients interviewed, none received any discussion of postoperative pain or pain control options. Ninety-three patients had no preemptive analgesia, and 23 had no postoperative analgesic in the first 48 hr. Severe acute postoperative pain is common in hospitals of developing countries but is much less common in Canadian hospitals.

Ketamine in LICs is inexpensive and readily available.^B Case reports of administering low-dose ketamine to surgical patients in African hospitals have shown improved pain management without complications or side effects.^{2,4} Many studies of ketamine in developed countries have used intravenous (IV) or subcutaneous (SC) infusions

with sophisticated electrical/electronic pumps that are not readily available in the hospitals of LICs.^{5,6} Meta-analysis of these methods showed overall efficacy and safety. A reduction in total opioid consumption and an increase in the time to first analgesic were observed across all studies ($P < 0.001$). Hallucinations and nightmares were more common with ketamine but sedation was not. When ketamine was efficacious for pain, postoperative nausea and vomiting was less frequent in the ketamine group.⁵ The greatest efficacy delivered was for severe pain, so we studied patients having major surgery (defined as surgery requiring a postoperative hospital stay of at least two days).

To avoid the need for syringe pumps, we used repeated SC injections. A single SC injection has several advantages in this setting. First, it provides a more prolonged and less peaked pharmacokinetic concentration profile than IV or intramuscular injections. Second, it requires only inexpensive and ubiquitous supplies. Lastly, it is easily taught to lay nursing assistants.⁷ This last consideration is important because of the limited nursing staff on the surgical wards of UTHK. We based the dose and injection intervals for this blinded randomized clinical trial (RCT) on a prior dose-finding study conducted using the same technique in the same hospital. That random-walk study found an acceptable dose of 0.9 mg·kg⁻¹ twice daily; however, we decided to simplify this to 1 mg·kg⁻¹.⁸

Hypothesis

We hypothesized that postoperative SC ketamine 1 mg·kg⁻¹ and 12-hr dosing intervals, determined in a prior dose-finding study conducted in the same hospital, can safely reduce postoperative pain in patients undergoing major surgery in Rwanda.

Methods

Trial design

The trial was designed as a blinded RCT with allocation concealment, parallel group design, and a 1:1 allocation ratio.

Participants

Participants were patients booked for major surgery, defined as surgery requiring admission to hospital for at least two days postoperatively.⁵ We did not attempt to recruit patients being rushed into the operating room from the emergency department. We approached patients whose names appeared on the “white board” as needing surgery

^A The World Bank categorizes Rwanda as a LIC, with per capita income of US\$700 in 2016. High-income countries have a gross national income per capita of US\$12,236 or more in 2016.

^B Less than Can\$40 per dose for drug, syringe, hypodermic needle, and alcohol swab.

when the next operating room and surgical team were available. Exclusion criteria included patients with seizure disorders, decreased cognitive function or psychosis, increased intracranial pressure, glaucoma, treatment for hypertension or hypotension, arrhythmias, inability to understand the consent process, refusal to participate in the study, allergy to ketamine, a history of narcotic abuse or dependence, ages younger than 18 and older than 65 yr, the use of regional or neuraxial anesthesia during surgery, and patients having surgery where the expectation was admission for less than two days.

Study setting

The Canadian anesthesia community has a close and ongoing educational initiative in Rwanda sponsored by the Canadian Anesthesiologists' Society International Education Foundation; consequently, we collaborated with the Department of Anesthesia at the University of Rwanda and conducted the study within the surgical services of UTHK.⁹

Interventions

Participants received standard care according to the clinical judgement of the surgeon, anesthesiologist, and nurses. Once a patient slated for major surgery consented to participate in the study, the participant number and weight were delivered to the hospital pharmacy in another building. The study pharmacist then used a computer-generated random number table, concealed from all other investigators, study nurses, caregivers, and participants, to prepare five syringes containing either ketamine $1 \text{ mg}\cdot\text{kg}^{-1}$ ("Ketamax-50"; ketamine $50 \text{ mg}\cdot\text{mL}^{-1}$; Troikaa Pharmaceuticals Ltd, Gujarat, India) or the equivalent volume of saline. Twenty-seven gauge hypodermic needles were attached to each syringe, placed in an envelope marked only with the participant number, and delivered to an investigator or study nurse in an area of the pharmacy outside the room where the syringes were prepared.

Participants in the ketamine group received five SC injections of ketamine $1 \text{ mg}\cdot\text{kg}^{-1}$ and the placebo group received an equivalent volume of saline. The injections were given at scheduled intervals—i.e., upon arrival in the postanesthesia care unit (PACU) following surgery, at 20:00 (if the participant arrived in the PACU prior to 16:00), and then every 12 hr thereafter until completion of five injections. The investigators or study nurses gave the injections after enquiring about pain severity and side effects. If the patient arrived in the PACU after 16:00, the second subcutaneous injection was administered at 8:00 on postoperative day (POD) 1 and every 12 hr thereafter until completion of the five injections in the evening of POD 2.

Outcomes

The primary outcome was the mean of daily pain scores on POD 1 and POD 2 on a validated 11-point verbal rating scale (VRS).¹⁰ Secondary outcomes were analgesic use and side effects obtained from patient, nurse, and chart. After the first injection, the study nurses and/or the investigators collected data prior to each subsequent injection. Sedation was measured at these times using the validated Richmond Agitation-Sedation Scale (RASS).¹¹ At noon on POD 1 and POD 2, the participants discussed the duration and quality of pain relief, and a nurse or investigator fluent in their language asked the participants about specific side effects, including hallucinations, dysphoria, nightmares, seizures, and nausea and vomiting. Patients were asked if side effects were mild, moderate, or severe. During the final contact, satisfaction was measured on a VRS scale of 0 to 10. Analgesic doses were recorded.

Sample size

Sample size calculation, with alpha significance of 0.05 and power of 0.8, was based on a clinically significant reduction of two points on the 11-point VRS and employed the standard deviation (SD) of 1.5 points found in the preliminary dose-finding study mentioned above. This yielded ten participants per arm. On the recommendation of the National University of Rwanda statistician, this was increased to 30 participants per arm to account for dropouts and unforeseen problems on a surgical service that was unaccustomed to randomized clinical trials.

Randomization

The simple random allocation sequence was computer generated by a research assistant in Saskatoon, Saskatchewan who played no role in enrolling participants and had no knowledge of the participants or of the assignment of participants to a group. Participants were enrolled by investigators or study nurses who also collected the data with no knowledge of allocation. A UTHK research pharmacist with no knowledge of the participants, other than a number and weight, and no further role in the investigation or care of the participants assigned participants to the interventions. Data were analyzed as "group A" or "group B" prior to unblinding as to which group received which treatment. Participants who withdrew before the first injection were excluded from analysis, and those who received at least one injection were analyzed by the intention-to-treat approach.

Allocation concealment

Concealment fails when a recruiter or investigator knows the next participant's group allocation and consciously or unconsciously chooses whether or not to recruit a prospective participant because their characteristics will increase the chance of a desired outcome. The person who generated the random allocation had no further knowledge of the study as it progressed and therefore could not indicate allocation to anyone else involved in the study. The pharmacist completed the allocation in a separate building out of sight of anyone involved and was instructed not disclose allocation to anyone involved in the study.

Blinding

Participants, investigators, data collectors, healthcare providers (i.e., surgeons, anesthesiologists, nurses, ancillary staff), and outcome adjudicators were blinded.

Similarity of interventions

The study drug and placebo saline were equivalent in volume, looked identical in the injecting syringe, and imparted no apparent difference in sensation when injected.

Baseline data

Age, sex, weight, and type of surgery were collected from the participants' charts. Height is not routinely measured at UTHK.

Ethical considerations

The study was approved by the National University of Rwanda Ethics Committee, the University of Saskatchewan Biomedical Research Ethics Board (Bio#14-193), and the Ethics Committee of the UTHK (EC/CHUK/11/15). In order to obtain informed consent prior to surgery, a fluently trilingual study nurse or physician explained the risks and benefits of the intervention to the patients in their most fluent language (English, French, or Kinyarwanda). It was made clear to the patients that they were free to decline participation in the study.

Patient safety

A Data Monitoring Committee (DMC) was established prior to the study to deal with ethical issues and safety. After data for 20 participants were collected (data categorized as group A and group B, but not which group was placebo and which was ketamine), a blinded

analyzer at the University of Saskatchewan planned interim analysis to address issues of safety, side effects, and efficacy of the dose. This interim analysis was to be presented to the DMC if there were severe or serious side effects (there were not). The DMC was to follow the following algorithm: 1) If the side effects were considered too severe or frequent, the DMC would unblind the study to see if the side effects were occurring in the placebo group or in the ketamine group. They would stop the study as they saw fit, and we would publish the results. 2) If it appeared that the chosen dose was too small to produce any effect, the DMC could recommend an increase in the dose. 3) If the interim analysis showed a large difference in pain scores between the two groups, the DMC would stop the study and we would publish the results.

Statistics

Statistical analysis was completed in SigmaPlot V. 11 or 13 (Systat Software, Inc. San Jose, CA, USA). The statistics program tested ratio data automatically for normality (Shapiro-Wilk test) and for equal variance (Brown-Forsythe test). Data passing these tests were compared by Student's *t* test, otherwise by Mann-Whitney rank-sum test. Categorical data were compared by a Chi square test or, if there were fewer than five in one or more categories, by Fisher's exact test. All *P* values are two-tailed. Verbal rating scale primary outcome data were treated as continuous ratio^C and analyzed in aggregate for POD 1 and POD 2. Furthermore, a comparison of total postoperative opioid consumption, converted to morphine equivalents, was conducted between the treatment and placebo groups. Because of the exploratory nature of the study, correction for multiple comparisons was not done. Ratio results are reported as mean (SD) with 95% confidence interval (CI). No subgroup or adjusted analysis was performed.

Results

Participant flow

See CONSORT flow sheet Fig. 1.¹²

Recruitment dates

Participants were recruited from January 1 to August 8, 2015.

^C Although VRS data are, strictly speaking, ordinal, in the pain literature, they are traditionally universally analyzed as if they were ratio.

Fig. 1 CONSORT flow diagram

Reason for ending trial

The trial ended when recruitment was complete.

Baseline data

Demographics are shown in Table 1, and analgesics and doses are shown in Table 2. Postoperative opioids were not different between groups, but more participants in the placebo group (28/29; 97%) received non-opioids compared with those in the ketamine group (18/30; 60%; $P = 0.001$). One participant in the placebo group received no postoperative analgesic whatsoever.

Numbers analyzed; losses and exclusions

All participants receiving any drug or placebo were included in an intent-to-treat analysis. Demographic data are shown in Table 1. Of the 69 patients approached, 61 were recruited; 32 were allocated to the ketamine arm and 29 to the placebo arm (see flow diagram Fig. 1). Two

patients reconsidered—one with fear of needles and one unable to communicate following mastoid surgery. These patients withdrew from the ketamine group prior to the first injection and were not analyzed. One patient withdrew on religious grounds after one injection in the placebo group and was included in the analysis. The DMC was not invoked. No participant required admission to the intensive care unit or postoperative ventilation.

Primary outcome

Verbal rating scale scores were obtained in 275 of the 295 specified times. For various logistical reasons, 20 scores were missing. Compared with the placebo group, the mean (SD) overall postoperative verbal rating pain score was less in the ketamine group [4.8 (1.7) vs 3.7 (1.5), respectively; difference of means, 1.1; 95% CI, 0.3 to 1.9; $P = 0.009$]. At every time point, patients given ketamine subcutaneously rated their pain lower than those who received placebo, with an overall significantly lower mean in the ketamine group. Median [interquartile range (IQR)] satisfaction was

Table 1 Demographics

	Ketamine	Placebo
Numbers (patients)	30	29
Age (yr)	35.3 (10.8)	42.2 (12.6)
Weight (kg)	57.7 (9.2)	57.3 (7.8)
Sex		
M	13	11
F	17	18
Surgery Type		
Abdominal	11	14
Gynecological	10	11
Orthopedic	4	0
Head & Neck	2	1
Plastic	3	3

Data are recorded as mean (standard deviation) or number

Table 2 Postoperative analgesics – total doses

Drug	Group	Patients given none	Mean dose	SD	Max	<i>P</i> value
Opioid*	Ketamine	6	18	23	84	0.52
	Placebo	6	17	16	84	
Acetaminophen (grams)	Ketamine	24	0.8	2	8	0.12
	Placebo	19	1.8	2.9	9	
Diclofenac (mg)	Ketamine	18	53	102	400	0.91
	Placebo	14	94	129	400	
Ibuprofen (mg)	Ketamine	28	83	446	2,400	1
	Placebo	28	89	377	1,600	

*Morphine equivalents (in mg) of fentanyl, meperidine, morphine, or tramadol. SD = standard deviation

not different between groups (ketamine: 7 [7–9]; placebo: 7 [6–8]; $P = 0.16$). For pain severity by incidence, see Fig. 2.

Fig. 2 Pain scores distribution. X-axis: verbal rating scale (VRS) pain scores. Y-axis: number of VRS assessments at each score. Bars: black = ketamine group; white = placebo group

Harms

Brief hallucinations (ketamine: 11 patients; placebo: 0 patients; risk difference, 0.37; 95% CI, 0.18 to 0.54; $P < 0.001$) were associated with ketamine administration (see Table 3). The participants rated all side effects as “mild”; none withdrew. In particular, all of the sedated patients were rousable. A RASS score of -1 (“drowsy but rousable by name with sustained wakefulness”) was not considered an adverse effect for patients during the first two days after major surgery. Clinically significant sedation occurred only in the ketamine group, with a RASS score of -2 (“light sedation – briefly awakens to voice with eye contact”) in three of 150 ($P = 0.09$) measurements and a score of -3 (“moderate sedation – any movement to voice but no eye contact”) in two of 150 measurements ($P = 0.16$). No sedation score was lower than -3 .

Table 3 Side effects

Side effect	Ketamine <i>n</i> (%)	Placebo <i>n</i> (%)	<i>P</i> value
Nausea or vomiting	2 (7%)	3 (10%)	0.66
Hallucination	11 (37%)	0 (0%)	< 0.001
Nightmare	2 (7%)	0 (0%)	0.49
Sedation	11 (37%)	1 (3%)	0.002
Hypertension	1 (3%)	0 (0%)	0.99

n = number

Discussion

The principal finding is that subcutaneous administration of ketamine 1 mg·kg⁻¹ (in addition to standard of care) on arrival in the PACU and thereafter every 12 hr reduced postoperative pain following major surgery in this low-resource setting. Hallucinations were more common in the ketamine group. Satisfaction was not different, but it is a poor measure of pain control or surgical experience.¹³

Postoperative analgesics are normally given in Canada both preemptively as regular standing orders and as needed in response to pain levels. The data reported in Table 3 suggest a different practice of postoperative analgesia in the UTHK; the great variance in opioid dose (standard deviations greater than means) is notable. The difference in the incidence of non-opioid analgesic use may have arisen in response to more pain in the placebo group. It also suggests that nurses turn to non-opioids for analgesia. Six participants in each group received no opioids whatsoever after major surgery, which would be unusual in Canada. We have undertaken an observational study of postoperative pain control in this hospital to attempt to clarify these issues.

Limitations

Weaknesses of the study are evident. First, a small sample size undermines the external validity. Second, the study is too small to declare SC ketamine safe when used in this way for postoperative pain control. Third, limited resources made it impossible to observe the times and extent of mobilization of the participants.

A further weakness of the study is that the sample size calculation was predicated on a VRS difference of two points, while we found a difference of only 1.1 points, albeit with a highly significant *P* value 0.009. Despite this small difference, analysis of pain severity categories (Fig. 2) shows that ketamine participants fell into the category of pain scores less than five far more frequently than placebo participants (70% vs 40%, respectively). This is clinically very important as it is the approximate level of

pain that allows for early mobilization.¹⁴⁻¹⁷ In searching for strengths and weaknesses in relation to other studies, we were unable to find studies similar enough for comparison.

Generalizability

A sample of all comers for major surgery is a strength of the study that makes the result more generalizable to a variety of surgical procedures than studies of specific surgical operations. Although our findings are likely transferable to other LICs, perioperative care may or may not be quite different elsewhere, and the study should be repeated in several other LICs before widespread implementation. It would appear to be applicable in conditions similar to those in the UTHK with careful tracking of outcomes.

Interpretation

The importance of the study emerges from the issue that postoperative pain is poorly controlled in LICs. Studies in Kenya and Nigeria revealed that 46-69% of patients rated pain after surgery as moderate to unbearable.¹⁸⁻²¹ The authors of these studies suggest that postoperative pain control could be improved with proper application of up-to-date information, improved training of healthcare providers, and access to suitable analgesics. A low number of adequately trained personnel has been cited as a major contributor to poor perioperative outcomes in developing countries.²² During the postoperative period, patients are largely under the care of overburdened nurses.²³ There is a paucity of literature describing the best practice, standards, and management strategies for postoperative pain control in LICs. What is known is that postoperative pain is often inadequately managed in these settings due to limited access to analgesics, a lack of human resources, and in some cases, a misunderstanding of pharmacology.^{20,24} It is notable that all of the cited studies of inadequate postoperative pain control are at least a decade old. The most recent, Size *et al.* 2007, besides our clinical experience in Rwanda, indicates that little has changed in the meantime.

We have found that subcutaneous administration of ketamine $1 \text{ mg} \cdot \text{kg}^{-1}$ is an effective means of providing postoperative analgesia. Moreover, it is inexpensive and easy to administer. This practice deserves further study as part of the postoperative pain control armamentarium for healthcare professionals in low-resource settings.

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References

- Brennan TJ, Kehlet H. Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain: not an easy path. *Anesthesiology* 2005; 103: 681-3.
- Famewo CE. Study of incidence of post-operative pain among Nigerian patients. *Afr J Med Med Sci* 1985; 14: 175-9.
- McQueen KA. Pain management: a global perspective. *Br J Anaesth* 2013; 111: 843-4.
- Batta SK. Low-dose ketamine analgesia for use in under-developed countries. *Anesth Analg* 2007; 104: 232.
- Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anesth* 2011; 58: 911-23.
- Safavi M, Honarmand A, Nematollahy Z. Pre-incisional analgesia with intravenous or subcutaneous infiltration of ketamine reduces postoperative pain in patients after open cholecystectomy: a randomized, double-blind, placebo-controlled study. *Pain Med* 2011; 12: 1418-26.
- Wilkinson GR. Pharmacokinetics. In: Hardman JG, Limbird LE, Gilman AG, editors. Goodman & Gilman's The Pharmacologic Basis of Therapeutics. 10th ed. NY: McGraw-Hill; 2001.
- Tuchscherer J, McKay WP, Twagirumugabe T. Low-dose subcutaneous ketamine for postoperative pain management in Rwanda: a dose-finding study. *Can J Anesth* 2017. <https://doi.org/10.1007/s12630-017-0914-0>.
- Enright A. Anesthesia training in Rwanda. *Can J Anesth* 2007; 54: 935-9.
- Heft MW, Gracely RH, Dubner R, McGrath PA. A validation model for verbal description scaling of human clinical pain. *Pain* 1980; 9: 363-73.
- Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; 289: 2983-91.
- Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2012; 10: 28-55.
- Godil SS, Parker SL, Zuckerman SL, et al. Determining the quality and effectiveness of surgical spine care: patient satisfaction is not a valid proxy. *Spine J* 2013; 13: 1006-12.
- Agostini PJ, Naidu B, Rajesh P, et al. Potentially modifiable factors contribute to limitation in physical activity following thoracotomy and lung resection: a prospective observational study. *J Cardiothorac Surg* 2014; 9: 128.
- Browning L, Denehy L, Scholes RL. The quantity of early upright mobilisation performed following upper abdominal surgery is low: an observational study. *Aust J Physiother* 2007; 53: 47-52.
- Dubljanin-Raspopovic E, Markovic-Denic L, Ivkovic K, et al. The impact of postoperative pain on early ambulation after hip fracture. *Acta Chir Iugosl* 2013; 60: 61-4.
- Arinzon Z, Gepstein R, Shabat S, Berner Y. Pain perception during the rehabilitation phase following traumatic hip fracture in the elderly is an important prognostic factor and treatment tool. *Disabil Rehabil* 2007; 29: 651-8.
- Faponle AF, Soyannwo OA, Ajayi IO. Post operative pain therapy: a survey of prescribing patterns and adequacy of analgesia in Ibadan, Nigeria. *Cent Afr J Med* 2001; 47: 70-4.
- Kolawole IK, Fawole AA. Postoperative pain management following caesarean section in University of Ilorin Teaching Hospital (UITH), Ilorin, Nigeria. *West Afr J Med* 2003; 22: 305-9.
- Ocitti EF, Adwok JA. Post-operative management of pain following major abdominal and thoracic operations. *East Afr Med J* 2000; 77: 299-302.
- Soyannwo OA. Post-operative pain control-prescription pattern and patients' experience. *West Afr J Med* 1999; 18: 207-10.
- Hodges SC, Mijumbi C, Okello M, McCormick BA, Walker IA, Wilson IH. Anaesthesia services in developing countries: defining the problems. *Anaesthesia* 2007; 62: 4-11.
- Size M, Soyannwo OA, Justins DM. Pain management in developing countries. *Anaesthesia* 2007; 62(Suppl 1): 38-43.
- Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg* 2007; 105: 205-21.