

COMPARATIVE STUDY OF THE EFFICACY OF INTRAVENOUS PARACETAMOL AND DEXMEDETOMIDINE ON POST-OPERATIVE ANALGESIC AND HEMODYNAMICS FOR PATIENTS UNDERGONE UPPER LIMB SURGERY

JAINAB PARWEEN*, FAHAD KHAN

Department of Anaesthesiology, Rama Medical College and Hospital and Research Centre, Hapur, Uttar Pradesh, India.

*Corresponding author: Jainab Parween; Email: jainialmaty@gmail.com

Received: 05 June 2023, Revised and Accepted: 18 July 2023

ABSTRACT

Objective: Comparative study of the efficacy of intravenous paracetamol and dexmedetomidine (DMED) on post-operative analgesic and hemodynamics for patients undergone upper limb surgery. Multimodal analgesia is recommended to reduce the stress response and prevent post-operative pain. Intravenous paracetamol and intravenous DMED are both effective components in respect of multimodal analgesia.

Methods: The present prospective randomized, double-blind, controlled study was performed on eighty American Society of Anesthesiologists (ASA) Grade I and Grade II physical status patients aged 18–65 years, of both genders, were selected for elective upper limb orthopedic surgical procedure under general anesthesia. Group P (paracetamol) patients were given 1 g paracetamol intravenously 30 min before surgery. Group D patients, 100 µg DMED/20 mL normal saline, was administered intravenously 30 min before surgery. Post-operative hemodynamic variables, post-operative pain scores (Visual Analogue Scale score), need for rescue analgesics and post-operative complication were recorded and treated accordingly.

Results: In both groups, females were in the majority with ASA grade I in the majority of the cases in both groups. Mean heart rate, mean arterial pressure, and Visual Analog Score for pain were comparable between the groups were compared at different time intervals (2, 4, 6, 12, 18, and 24 h) ($p > 0.05$). Regarding complications Nausea, vomiting, itching and stomach irritation was in 17.5%, 15.0%, 7.5% and 20.0% for group D and for group P nausea and vomiting was in 15.0% and 10.0% and no other complication occurs in group D.

Conclusion: Pre-emptive administration of paracetamol is a cost-effective and safe method of providing post-operative analgesia for patients undergoing upper limbs surgery.

Keywords: Paracetamol, Dexmedetomidine, Hemodynamics, Post-operative pain, Analgesia.

© 2023 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2023v16i8.48998>. Journal homepage: <https://innovareacademics.in/journals/index.php/ajpcr>

INTRODUCTION

Orthopedic surgeries, especially on the upper extremities, are one of the most common surgical procedures [1]; that could be done under the peripheral nerve blocks [2]. One of the main concerns for surgical operations under local blocks along with other factors is the duration of post-operative analgesia and hemodynamic stability (changes in blood pressure and heart rate [HR]) [3]. Several studies have been done on the use of supplements with local anesthetics to improve block quality and increase post-operative analgesic time [4] and hemodynamic stability [5]. One of the medications recently studied for this reason is dexmedetomidine (DMED) [5]. DMED is an alpha 2-specific agonist that has known sedative and analgesic effects [6]. Some studies have been reported improvement in the quality of spinal and epidural anesthesia by adding it to local anesthetic drugs [7]. The use of this drug in the peripheral nervous system and its effects on block quality and analgesia also have recently been considered [8]. On the other hand, some studies have been mentioned the positive effects of intravenous DMED administration on hemodynamic stability in the course of general anesthesia (GA) [9]. Some studies also showed that adding it as a supplement to local anesthetics during brachial plexus block could significantly prolong the duration of analgesia [8]. However, one study has been demonstrated that adding DMED to high volumes of local anesthetics may reduce its analgesic features since its analgesic effect is concentration dependent [10]. A remarkable point in the mentioned studies is that DMED has always been used as an adjunct to local anesthetics.

Relief of post-operative pain represents one of the clinical areas in which precise standardization does not exist despite published data. It's still incompetently relieved despite the substantial improvements in knowledge of the mechanisms and the treatment of pain. Different treatments have been proposed to relieve the pain after orthopedic surgery. Administration of analgesics before surgery is used by many as the method of reducing post-operative pain. Pre-emptive analgesia is an antinociceptive procedure that prevents the production of afferent feedback lateral processing that amplifies post-operative pain [11]. Therefore, it is important to start analgesia before surgery, which would cover the surgery and initial post-operative period. Studies have shown that besides relieving the pain, this also decreases the length of intensive care or hospital stay and morbidity [12].

A multimodal analgesic regimen including opioids, acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), and the local anesthetics could be administered either alone, or in combination to attain adequate analgesia without the untoward side effects [13]. American Society of Anesthesiologists (ASA), acute pain management guidelines state that the clinicians must use multi-modal analgesia whenever possible in perioperative setting. ASA recommends that all the surgical cases receive around the clock regimen of the acetaminophen, and NSAID unless they contraindicated and dosages, and duration of the therapy must be individualized, considering the efficacy with risk of adverse events [14].

Paracetamol is one of the most widely used drugs for the treatment of fever and pain. It is used preoperatively in oral, rectal, and parenteral

formulations. It is still not confirmed whether it acts peripherally and/or centrally and it acts on which analgesic pathway. Because of its efficacy, safety, lack of clinically significant drug interactions, and lack of adverse effects associated with other analgesics, intravenous (IV) paracetamol is an important component of a multimodal analgesic treatment plan [15].

The use of IV paracetamol as analgesia, using an opioid as a rescue analgesic only when needed, would reduce the amount of opioid used and ensure a comfortable post-operative recovery period. Paracetamol is a non-opioid drug that is being used in the perioperative period [16]. Paracetamol is one of the most ubiquitous drugs in hospitals and community settings.

Paracetamol has been found to be a useful antipyretic and moderately potent analgesic across various conditions, patient populations, and circumstances. The remarkable tolerability and lack of serious side effects at clinical doses explain its popularity. With the introduction of a stable intravenous (IV) formulation of Paracetamol (PERFALGAN), it is now possible to use its analgesic effect in perioperative patients.

DMED, a highly selective α_2 -adrenergic agonist, is the most preferred sedative because of its advantages. One of these is conscious sedation with minimal respiratory depression, enabling the patients to be more cooperative during the intervention. DMED also manifests sympatholytic, sedative, hypnotic, amnesic, and analgesic properties. Consequently, DMED is increasingly used for procedural sedation during intervention, sedation in intensive care patients with mechanical ventilation, and as an adjuvant in balanced anesthesia. It is well known that the pharmacologic effect of DMED in the cardiovascular system includes the reduction of blood pressure and HR in a dose-dependent manner by activating the peripheral α_2 -adrenoreceptor [17]. Indeed, the occurrence of hemodynamic instability after DMED administration, including hypotension or bradycardia, has been reported in several investigations. Reported incidence of hemodynamic instability in intensive care units (ICU) ranges from 20.6% to 71% [18].

Numerous meta-analyses demonstrate the effectiveness of DMED for post-operative pain control [19,20]. In a 2012 meta-analysis of 1792 cases, DMED reduced opioid consumption by 30.0% at 24 h post-operatively [19]. DMED has a stronger analgesic effect compared to clonidine, and acetaminophen but weaker than the ketamine, or NSAID [19]. This not only makes the DMED an attractive agent for ERAS but also for the chronic pain cases [21]. In a 2015 meta-analysis, although the DMED reduced the pain intensity, the opioid consumption, and post-operative nausea and vomiting, it had no effect on recovery time [22].

METHODS

The present prospective randomized, double-blind, controlled study was performed on eighty ASA Grade I and Grade II physical status patients aged 18–65 years, of both genders were selected for elective upper limb orthopedic surgical procedure under GA. The exclusion criteria were patients with evidence of any contraindication to brachial block such as neurological, psychiatric, neuromuscular, bleeding problems, pneumothorax, diabetes, and pregnancy. The trial has been registered prospectively with the clinical trial registry of India. This study was conducted between January 2022 and July 31, 2023. Written informed consent was obtained from all patients.

Complete blood count, coagulation profile, renal/liver function tests, X-ray chest, and electrocardiogram were normal. Patients admitted for either unilateral, or bilateral upper limb (humerus, shoulder, and elbow) surgical procedures. Cases having allergic reactions to medications, major organ disease, coagulopathy, gastric ulcer complaints, psychiatric, or neurological disorders, drug, or alcohol addiction excluded. Alprazolam 0.25 mg and pantoprazole 40 mg tablets perorally were given at bedtime as pre-medication. Intra-venous infusion line started with ringer lactate 60 min before commencement of anesthesia. In pre-operative holding area, cases were assigned randomly to one study

group using random number (n=40 in each). Involved anesthesiologist kept uninformed of group allocated, and medication given to them as per study protocol. Group-P patients were given intra-venous g paracetamol diluted in 100 mL of 0.90% normal saline (NS) covered with opaque sheet, half hour before surgical procedure. In Group-D patients, 100 μ g DMED/20 mL NS, was administered intravenously 30 min before surgery.

All patients were induced with fentanyl 2 mcg/kg, sodium thiopentone 5 mg/kg, and succinylcholine 2 mg/kg intravenously. Neuro-muscular relaxation was achieved with the non-depolarizing muscle relaxant atracurium besylate 0.5 mg/kg, and the top-up dose was 1/4th of the loading dose at irregular intervals. Anesthesia was maintained to oxygen, nitrous-oxide mixture (40:60), and isoflurane (0.5–1.0%) delivered by IPPV using circle absorber system. The residual neuro-muscular block reversed with neostigmine 0.05 mg/kg, and glycopyrrolate 0.01 mg/kg. The intra-operative pain was evaluated by evaluating hemodynamic variables (involuntary increase in the HR, and blood pressure). Post-operative pain valuation was done at the different time intervals; 1 h, 2 h, 4 h, 6 h, 12 h, 18 h and 24 h using visual analog scale (VAS) ranging from 0 to 10 mm. Rescue analgesia given as fentanyl 1 mcg/kg or 50 mcg IV if VAS score was >3. Post-operative complication documented, and treated accordingly.

The statistical data were analyzed using SPSS software (version 20.0, SPSS, Inc., Chicago, IL, USA) Software, and presented in mean (SD), frequency, percentage, and median (range) as appropriate. Comparative evaluation between group-D and -P was done using 2 \times 2 contingency table by Student's t-test, the Chi-square test or the Fisher's exact test. $p < 0.05$ was considered significant.

OBSERVATION AND RESULTS

A total of 80 cases were included in the study, which were equally divided into two groups with 40 cases each. Group P cases were administered with paracetamol, whereas group D was given 100 μ g DMED/20 mL NS, which was administered intravenously 30 minutes before surgery. Mean age of studied cases was 41.75 \pm 11.64 years for group P and 44.88 \pm 10.62 years for group D which was significantly higher than group P ($p < 0.05$). In both groups females were in majority with ASA grade I in majority of the cases in both groups. Mean HR, mean arterial pressure, and Visual Analog Score for pain were comparable between the groups were compared at different time interval (2, 4, 6, 12, 18, and 24 h) ($p > 0.05$). Regarding complications, nausea, vomiting, itching, and stomach irritation was in 17.5%, 15.0%, 7.5%, and 20.0% for group D and for group P, nausea and vomiting were in 15.0% and 10.0%, and no other complication occurs in group D.

DISCUSSION

In this current prospective randomized, double-blind, controlled study a total 80 cases were included which were equally divided in two groups with 40 cases each. Group P cases were administered with 1g paracetamol, whereas group D was given 100 μ g DMED/20 mL NS, was administered intravenously 30 min before surgery. The mean age of studied cases was 41.75 \pm 11.64 years for group P and 44.88 \pm 10.62 years for group D. In both the groups females were in majority with ASA grade I in majority of the cases in both groups. In a similar study, Jan *et al.* [23] also opted similar methodology their respective study and reported the age, BMI, male to female ratio and duration of the surgery were similar in both groups.

According to New South Wales Therapeutic Advisory Group Current Opinion October 2005, the recommended dose of Paracetamol is 1 g IV up to 4 times daily with a minimum interval between each dose of at least 4 h in adults [24]. At recommended dosages Paracetamol is not associated with increased occurrence of nausea, vomiting and respiratory depression with opioids. Furthermore, paracetamol, because of its different mechanism of action interferes neither with platelet nor kidney function. Its analgesic action is not clear although

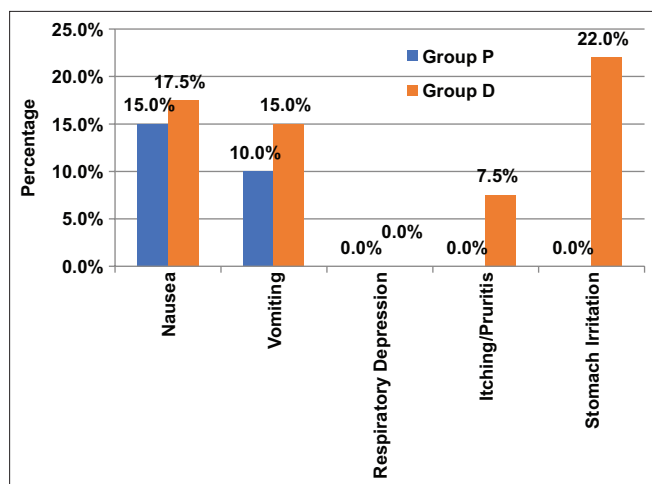


Fig. 1: Comparison of side effects observed in both groups

Table 1: Demographic parameters of the studied patients

Variables	Group P (n=40) Mean±SD	Group D (n=40) Mean±SD	p-value
Age (years)	41.75±11.64	44.88±10.62	0.212*
Weight (kg)	64.85±6.22	64.90±6.85	0.972*
Height (m)	1.61±0.060	1.62±0.059	0.454*
BMI (kg/m ²)	24.78±2.61	24.64±2.75	0.816*
Operation duration (min)	78.52±21.33	89.32±25.23	0.224*
Sex			
Male	15 (37.5%)	13 (32.5%)	0.639**
Female	25 (62.5%)	27 (67.5%)	
ASA Grade			
I	26 (65%)	23 (57.7%)	0.491**
II	14 (35%)	17 (42.5%)	

*Independent Sample t test; **Chi-square test; P<0.001=statistically highly significant; P<0.05=statistically significant, P>0.05=statistically non-significant

Table 2: Comparison of mean heart rate in two groups at different time interval

	Group P (n=40) Mean±SD	Group D (n=40) Mean±SD	p-value
Baseline	80.50±4.98	82.38±8.65	0.239
Post-operative 2 h	82.13±5.40	83.33±9.44	0.488
Post-operative 4 h	83.53±3.64	84.28±6.05	0.504
Post-operative 6 h	85.85±10.22	83.98±9.23	0.392
Post-operative 12 h	91.38±5.93	90.75±5.53	0.628
Post-operative 18 h	89.98±4.04	89.88±8.39	0.946
Post-operative 24 h	87.75±4.30	89.53±8.37	0.236

Independent sample t-test

its central level action has been hypothesized [25]. Because of the lower adverse events compared to NSAIDs, paracetamol be the preferred choice for peri-operative baseline analgesia [26]. Paracetamol does enhance analgesic efficacy when added to NSAIDs compared to NSAIDs alone.

DMED, and α-2 adrenoreceptor agonist is approved for sedation of initially intubated and mechanically ventilated patients by continuous infusion for only <24 h in the intensive care setting. α-2 adrenoreceptor agonists are being increasingly used in anesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anesthesia, and surgery; but also cause sedation, analgesia, and anxiolysis. The bolus of 1 µg/kg DMED results initially in transient increase of blood pressure, and reflex fall in HR, particularly in younger, healthy patients [27]. Given the propensity of the drug

Table 3: Mean arterial pressure analysis in respective time interval among the groups

MAP	Group P (n=40) Mean±SD	Group D (n=40) Mean±SD	p-value
Baseline	88.90±4.36	88.19±5.08	0.874
Post-operative 2 h	82.40±5.28	81.74±5.29	0.616
Post-operative 4 h	85.07±5.05	84.28±5.44	0.641
Post-operative 6 h	85.58±4.91	85.73±4.94	0.784
Post-operative 12 h	88.43±3.43	87.92±4.15	0.811
Post-operative 18 h	90.93±3.93	90.43±4.62	0.891
Post-operative 24 h	90.26±3.98	89.73±4.62	0.716

Independent sample t-test

Table 4: Comparison of pain visual analogue scale in both groups at different time interval

VAS	Group P (n=40) Mean±SD	Group D (n=40) Mean±SD	P value
Post-operative 2 h	2.35±2.16	2.33±0.94	0.947
Post-operative 4 h	2.40±1.29	2.55±1.15	0.586
Post-operative 6 h	2.13±1.34	2.10±0.841	0.921
Post-operative 12 h	1.83±1.76	1.83±0.874	1.00
Post-operative 18 h	1.80±1.36	1.63±0.925	0.504
Post-operative 24 h	1.60±1.43	1.23±0.620	0.132

Independent sample t-test

to produce hypotension and or bradycardia when it is administered to volunteers or patients, it was important to determine an infusion rate that would maximize the anesthetic and analgesic sparing effect although, minimizing the occurrence of adverse cardiovascular side-effects requiring therapeutic intervention. Jung *et al.* [28] in their study depicted significant advantage of the DMED at the dose of 1 µg/kg bolus followed by 0.2–0.7 µg/kg/h infusion for 24 h. It is safe sedative substitute to benzodiazepine/opioid combination in cases undergoing monitored anesthesia-care for multitude of procedures due to its analgesic, “co-operative sedation” and lack of the respiratory depression properties [29]. Several findings lead to the conclusion that the major sedative, and anti-nociceptive effects of the DMED are attributable to the stimulation of α-2 adrenoreceptors in locus coeruleus.

In our study, at a dose of 1 g paracetamol diluted in the 100 ml of 0.90% NS and 100 µg DMED/20 mL NS infusion before 30 min, the surgical procedure had insignificant mean HR, mean arterial pressure, and Visual Analog score for pain were comparable between groups were compared at different time interval (2, 4, 6, 12, 18, and 24 h) (p>0.05) which corroborates with study of Jung *et al.* [28] in randomized double-blind compared effects of DMED, and remifentanyl on the hemodynamic stability, sedation, and post-operative pain in PACU with DMED at the dose of 1 µg/kg IV over 10 min followed by 0.2–0.7 µg/kg/h continuous IV infusion had significant advantage regarding post-operative hemodynamic stability. Cattabriga *et al.* [25] administered 1g paracetamol premedication, and highlighted fact that the paracetamol has good analgesic action studying 1st 30 h deep breathe VAS score, which were lower significantly. In a study by Joshi *et al.*, [30] it had been observed that pre-operative dosage of the analgesics produced significant reduction in post-operative pain within 2–4 h treatment Pre-operative analgesics significantly reduced the opioid consumption in the orthopedic surgeries. Our result was comparable to another studies [31-33].

The present study noted that the post-operative complications of nausea, vomiting, itching, and stomach irritation were in 17.5%, 15.0%, 7.5%, and 20.0% for group D and for group P nausea and vomiting was in 15.0% and 10.0%, and no other complication occurs in group P. In contrast to our study, Jan *et al.* [23] reported that nausea and vomiting were reported in 2 (6.67%) in Group-D and 3 (10.0%) in Group-P; difference was not significant. No patient had renal profile dysfunction in post-operative period.

The study has some limitations. First, inter-individual variability was not controlled in the study. Hypo-albuminemia and lower cardiac output are suggested to induce prolonged DMED effects in critically ill patients [34]. DMED has high protein binding competence, with 94.0% of it bound to the albumin, and α 1-glycoprotein. Hypo-albuminemia can therefore be expected to affect drug's pharmacokinetics [17,34]. However, all the enrolled participants in current study were healthy patients with ASA/PS I-II. Subjects in critical medical conditions were excluded from the study.

CONCLUSION

According to the findings of the current research, IV paracetamol, when administered 30 min before surgery, was successful in reducing the post-operative VAS score, and the analgesic demand, and can be considered an effective and safe alternative for post-operative analgesia. In addition, it helps to attenuate the hemodynamic changes that are involved with having an upper limb procedure done. Hence, IV paracetamol can be used as an effective method for post-operative analgesia with the least possible side effects.

REFERENCES

- Jain NB, Higgins LD, Losina E, Collins J, Blazar PE, Katz JN. Epidemiology of musculoskeletal upper extremity ambulatory surgery in the United States. *BMC Musculoskelet Disord* 2014;15:4.
- Brattwal M, Jildenstål P, Warrén Stomberg M, Jakobsson JG. Upper extremity nerve block: How can benefit, duration, and safety be improved? An update. *F1000Res* 2016;5:F1000 Faculty Rev-907.
- Bruce BG, Green A, Blaine TA, Wesner LV. Brachial plexus blocks for upper extremity orthopaedic surgery. *J Am Acad Orthop Surg* 2012;20:38-47.
- Bharti N, Sardana DK, Bala I. The analgesic efficacy of dexmedetomidine as an adjunct to local anesthetics in supraclavicular brachial plexus block: A randomized controlled trial. *Anesth Analg* 2015;121:1655-60.
- Patel CR, Engineer SR, Shah BJ, Madhu S. Effect of intravenous infusion of dexmedetomidine on perioperative haemodynamic changes and postoperative recovery: A study with entropy analysis. *Indian J Anaesth* 2012;56:542-6.
- Helander EM, Menard BL, Harmon CM, Homra BK, Allain AV, Bordelon GJ, *et al*. Multimodal analgesia, current concepts, and acute pain considerations. *Curr Pain Headache Rep* 2017;21:3.
- Kaur S, Attri JP, Kaur G, Singh TP. Comparative evaluation of ropivacaine versus dexmedetomidine and ropivacaine in epidural anesthesia in lower limb orthopedic surgeries. *Saudi J Anaesth* 2014;8:463-9.
- Marhofer D, Kettner SC, Marhofer P, Pils S, Weber M, Zeitlinger M. Dexmedetomidine as an adjuvant to ropivacaine prolongs peripheral nerve block: A volunteer study. *Br J Anaesth* 2013;110:438-42.
- Panchgar V, Shetti AN, Sunitha HB, Dhulkhed VK, Nadkarni AV. The effectiveness of intravenous dexmedetomidine on perioperative hemodynamics, analgesic requirement, and side effects profile in patients undergoing laparoscopic surgery under general anesthesia. *Anesth Essays Res* 2017;11:72-7.
- Brummett CM, Padda AK, Amodeo FS, Welch KB, Lydic R. Perineural dexmedetomidine added to ropivacaine causes a dose-dependent increase in the duration of thermal antinociception in sciatic nerve block in rat. *Anesthesiology* 2009;111:1111-9.
- Hogan QH. No preemptive analgesia: Is that so bad? *Anesthesiology* 2002;96:526-7.
- Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of postoperative pain. *Br J Anaesth* 1993;70:434-9.
- Woolf CJ, Chong MS. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993;77:362-79.
- American Society of Anaesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of anesthesiologists task force on acute pain management. *Anesthesiology* 2012;116:248-73.
- Groudine S, Fossum S. Use of intravenous acetaminophen in the treatment of postoperative pain. *J Perianesth Nurs* 2011;26:74-80.
- Sinatra RS, Jahr JS. Efficiency and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopaedic surgery. *Anesthesiology* 2005;102:822-31.
- Weerink MA, Struys M, Hannivoort LN, Barends CR, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet* 2017;56:893-913.
- Ice CJ, Personett HA, Frazee EN, Dierkhising RA, Kashyap R, Oeckler RA. Risk factors for dexmedetomidine-associated hemodynamic instability in noncardiac intensive care unit patients. *Anesth Analg* 2016;122:462-9.
- Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic α 2 agonists on postoperative morphine consumption and pain intensity: Systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2012;116:1312-22.
- Tsaousi GG, Pourzitaki C, Aloisio S, Bilotta F. Dexmedetomidine as a sedative and analgesic adjuvant in spine surgery: A systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol* 2018;74:1377-89.
- Tumber PS. Optimizing perioperative analgesia for the complex pain patient: Medical and interventional strategies. *Can J Anesth* 2014;61:131-40.
- Le Bot A, Michelet D, Hilly J, Maesani M, Dilly MP, Brasher C, *et al*. Efficacy of intraoperative dexmedetomidine compared with placebo for surgery in adults: A meta-analysis of published studies. *Minerva Anestesiol* 2015;81:1105-17.
- Jan M, Singh G, Zarfishan A, Gupta R, Kumar U. Pre-emptive analgesic efficacy of intravenous diclofenac versus paracetamol in orthopedic surgery. *Bahrain Med Bull* 2021;43:354-6.
- New South Wales Therapeutic Advisory Group Inc. IV Paracetamol- where does it sit in hospital practice? *Curr Opin* 2005;4:1-8.
- Cattabriga I, Pacini D, Lamazza G, Talarico F, Di Bartolomeo R, Grillone G, *et al*. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: A double blind randomized controlled trial. *Eur J Cardiothorac Surg* 2007;32:527-31.
- Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: A qualitative review. *Br J Anaesth* 2002;88:199-214.
- Bhatia P. Dexmedetomidine: A New Agent in Anaesthesia and Critical Care Practice; 2002. Available from: https://www.theiaforum.org/article_folder/dexmedetomidine-anaesthesia-critical-care-practice.pdf
- Jung HS, Joo JD, Jeon YS, Lee JA, Kim DW, In JH, *et al*. Comparison of an intraoperative infusion of dexmedetomidine or remifentanyl on perioperative haemodynamics, hypnosis and sedation, and postoperative pain control. *J Int Med Res* 2011;39:1890-9.
- Grewal A. Dexmedetomidine: New avenues. *J Anaesthesiol Clin Pharmacol* 2011;27:297-302.
- Joshi GP, Viscusi ER, Gan TJ, Minkowitz H, Cippolle M, Schuller R, *et al*. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral COX-2 specific inhibitor. *Anesth Analg* 2004;98:336-42.
- Savitha KS, Dhanpal R, Kothari AN. The effect of multimodal analgesia on intraoperative morphine requirement in lumbar spine surgeries. *Anesth Essays Res* 2017;11:397-400.
- Simon E, Bánk J, Gál J, Siró P, Novák L, Fülesdi B, *et al*. Administration of preemptive analgesia by diclofenac to prevent acute post craniotomy headache. *Ideggyogy Sz* 2012;65:302-6.
- Nesek-Adam V, Grizelj-Stojčič E, Mršič V, Rašić Z, Schwarz D. Preemptive use of diclofenac in combination with ketamine in patients undergoing laparoscopic cholecystectomy: A randomized, double-blind, placebo-controlled study. *Surg Laparosc Endosc Percutan Tech* 2012;22:232-8.
- Iirola T, Ihmsen H, Laitio R, Kentala E, Aantaa R, Kurvinen JP, *et al*. Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. *Br J Anesth* 2012;108:460-8.