INTERNATIONAL JOURNAL OF SCIENCE AND NATURE

www.scienceandnature.org

INTRAVENOUS PARACETAMOL INFUSION CAN PROLONG DURATION OF SPINAL ANESTHESIA IN PATIENTS UNDERGOING MAJOR GYNECOLOGICAL SURGERIES

Dipasri Bhattacharya, Sankar Roy, Swati Sribastav, Ranabir Chanda, Swarup Paul, Goutam Chowdhury & Asim Kundu
Department of Anesthesiology, R. G. Kar Medical College, Kolkata, India

ABSTRACT
Intravenous infusion of paracetamol is recently being used widely for pain control during intra-operative as well as post-operative period. Paracetamol is primarily thought to be cyclooxygenase inhibitor acting through the central nervous system. This study was designed to evaluate the effect of single pre-operative intravenous infusion of paracetamol on spinal blockade in patients undergoing major gynecological surgery. One hundred ASA I and II patient aged 30-60 years undergoing elective major Gynecological surgery under spinal anesthesia were included in this randomized double blind study. The patients were randomly allocated to receive either 1 gm/100 ml paracetamol Group A (n=50) or 100 ml normal saline Group B (n=50) 30 minutes before administration of spinal anesthesia. Onset and duration of sensory and motor block, regression of sensory block, and quality of motor block were recorded. Intensity of pain was assessed by Visual Analogue Scale (VAS) Score. Time of rescue analgesic administration was also recorded. Duration of analgesia was longer in group A (intravenous paracetamol) compared to group B (placebo). Sensory regression was also delayed in group A. VAS was lower all the time in group A compared to group B. The result was statistically significant ($p<0.05$). The result showed that Intravenous paracetamol infusion prolonged the duration and intensity of spinal anaesthesia following major gynecological surgery.

KEY-WORDS- Intravenous paracetamol, Spinal anesthesia, major Gynecological surgery.

INTRODUCTION

Spinal anesthesia is widely practiced for major Gynecological sugery for quite a long time. Different adjuvant has been used to prolong the duration of spinal anesthesia, among them nonsteroidal anti-inflammatory drugs are most commonly used. Paracetamol a non-opioid drug, was synthesized in 1878 by Morse and introduced for medical usage in 1893.It has been used peri-operatively in oral, rectal and parenteral formulations and it is believed that it primarily acts upon the central nervous system by cyclooxygenase inhibition, and probably has an indirect influence on the serotoninergic system. Oral, intramuscular and rectal administration of paracetamol for pain relief is a common practice. However, there are paucity of studies of the use of intravenous paracetamol before spinal anesthesia. In this prospective, randomized, double blind, placebo-controlled clinical study, we assessed the effect of paracetamol infusion on the duration of analgesia, sensory regression during spinal anesthesia, intensity of analgesia by VAS score and requirement of rescue analgesic in the postoperative period . The adverse effects and patient satisfaction score were also noted. Our study ended with requirement of rescue analgesic on patient demand or VAS > 4.

METHOD

After obtaining approval of the institutional ethics committee and written informed consent from the patients, a randomized double blind study was undertaken with 100 ASA I-II women, aged between 30 to 60 years, scheduled for elective major gynecological surgeries under spinal anesthesia. Patients with known contraindication to spinal anesthesia, the study drug, patients with a history of hepatic, renal, cardiopulmonary disease, hypertension, diabetes, asthma were excluded.

Intravenous access was secured with 18G cannula. Standard routine monitoring like electrocardiogram, non-invasive blood pressure, and pulse oximetry were used to monitor all patients. Spinal anesthesia was administered with 25 G Quincke Spinocaine needle at L_3-L_4 space through standard midline approach with the patient at sitting posture with 3.0 ml (0.5%, 15 mg) hyperbaric bupivacaine. If the spinal block failed; the procedure was abandoned, and general anesthesia was administered and those patients were excluded from the study.

The patients were randomized to one of the two groups based on a computer generated random number list. Group P (n=50) received 1gm/100 ml paracetamol over 15 minutes and Group C received 100 ml. of Normal Saline as placebo over 15 minutes before administration of spinal anesthesia. The study solution to be given to the patient was concealed in a sealed envelope bearing the patient number was handed over to the anesthetist not involved in the study. Patients and investigators were blinded to the identity of study treatment. Ringer's lactate 500ml was infused rapidly within half an hour then 500 ml hourly till 2 hours, followed by 500ml Ringer's solution : DNS 1:2 ratio 4hourly till 24 hours.Sensory block was assessed by pinprick, cold alcohol swap in midclavicular line bilaterally by a blind assessor in a cephalad to caudal direction with a disposable dermatome tester at 10, 30, mins, 1,2,3,4 hours after injection of spinal drugs for

dermatomal distribution of sensory block analysis. When block height reached up to T_6 dermatome surgery was started. Post-operative pain was assessed by the patient using the visual analogue scale (VAS- 0= No pain, 10= worst possible pain) at 2,4,8,12 hour. Duration of sensory blockade was considered till the demand of analgesic or a VAS score >4 or on patient demand. Motor block was tested with Modified Bromage Scale. Motor block duration was the time for return to Bromage Scale 1.All durations were calculated considering the time of completion of spinal injection as time zero.

Patients with a VAS Score recording >4 were given rescue analgesic (75 mg Diclofenac intravenously).The time for the first administration of post-operative analgesia and the number of patients who required rescue analgesic were recorded. The total analgesic consumption was noted over first 12 hours along with dermatomal regression at 10 mins, 30 mins,1 hour, 2 hour and 3 hour by an independent anesthesiologist. Undesired effects if any and patient satisfaction scale were recorded on a 3 point scale (3-excellent, 2-good, 1-poor).

To calculate the sample size, we considered the duration of analgesia (defined as time of administration of spinal analgesia until the demand of rescue analgesic) as primary outcome measure. It was estimated that 49 subjects per study group were required to detect a difference of 60 minutes in this parameter with 90% power and 5% probability of Type 1 error. This calculation assumed Standard Deviation (SD) of 90 minutes for this study.

RESULTS

Vassar Stats Statistical ComputationWebsite (Vassar College, USA, www. faculty.Vassar.edu/lowery/Vassar Stats. html) were used to analyze all data statistically. Age, height, weight ,duration of surgery ,onset of sensory and motor block, duration of sensory and motor block, VAS score, time of demand of rescue analgesic, total consumption of rescue analgesic were compared using unpaired 't' Test. ASA status were compared with Chi-square test. Types of operation and dermatomal distribution at specified times were compared using Fisher's Exact Probability Test with Freeman-Halton Extension. Data were presented as mean ±SD. Significance was determined at $p<0.005$. One hundred patients were included in the study (50- paracetamol Group, 50- Normal Saline or Control Group). Pre-operative characteristics and intra-operative data did not differ significantly between the groups (Table-1).

TABLE-1 Patient characteristics

	Group P n= 50 Paracetamol	Group C n=50 Normal Saline
Age (years)	45.2±4.7	46.5±7.2
Height (cm)	155.4±4.1	156.9±4.3
Weight (kg)	56±4.6	55.9±5.01
ASA physical status (I:II)	40:10	40:10
Duration of surgery (minutes)	98.6±13.1	100.1±14.7

TABLE 2. Types of Operation performed in both groups.

Nature of Operation	Group P n=50 Paracetamol	Group C n=50 Normal Saline
Abdominal Hysterectomy+ BSO	30	28
Vaginal Hysterectomy +PFR	2	5
Vaginal Hysterectomy	5	4
Ward Mayo's Operation	13	13

TABLE 3. Onset of Sensory and motor block and their duration of effect between both groups.

	Group P n=50 Paracetamol	Group C n=50 Normal Saline	
Onset of Sensory block(minutes)	2.0±0.5	2.1±0.5	not significant
Onset of Motor Block(minutes)	3.5±0.4	3.3±0.4	not significant
Duration of Sensory block(hours)	8.50±0.5	4.25±0.3	p<0.001,significant
Duration of Motor Block(hours)	3.3±0.3	3.0±0.3	not significant

No significant difference in operative procedures among the groups was noted. (Table-2). Onset of sensory as well as motor block in both the groups are quite comparable whereas the duration of sensory block were significantly higher in paracetamol group ($p<0.001$) though duration of motor block were comparable among the groups. (Table-3). The evolution of pain intensity displayed difference among the groups ; in paracetamol group the pain intensity

increases over hours and reached a score of 4 after 8 hours whereas in control group it reached a score of 4 after 4 hours after operation.VAS Scores at 0 and 4 hour were significantly lower in paracetamol Group ($p<0.001$). As the VAS approached above 4 in Group C after 4 hours rescue analgesia was administered, therefore VAS dropped in Group C significantly in comparison to Group P (Figure-1). VAS Score in Group P reached a Score above 4 after 8 hours where rescue analgesia was given and VAS Score at 12 hour were significantly lower in Group P. Dermatomal distribution of height of sensory block between both the groups was comparable up to 30 minutes after spinal injection. Sensory regression were significant($p=0.002$) at 1 hour when 40 patients of paracetamol group and 20 patients of control group were in T_{6-8} ,and10 patients of paracetamol group and 30 patients of control group were in T_{8-10}.Similarly dermatomal regression were statistically significant at 2 hours and 3 hours also. Even after 3 hours of spinal injection, all patients of paracetamol group showed sensory analgesia up to T_{7-8}level, whereas in 10 patients of control group the level dropped below T_{8-10} (Table-4).

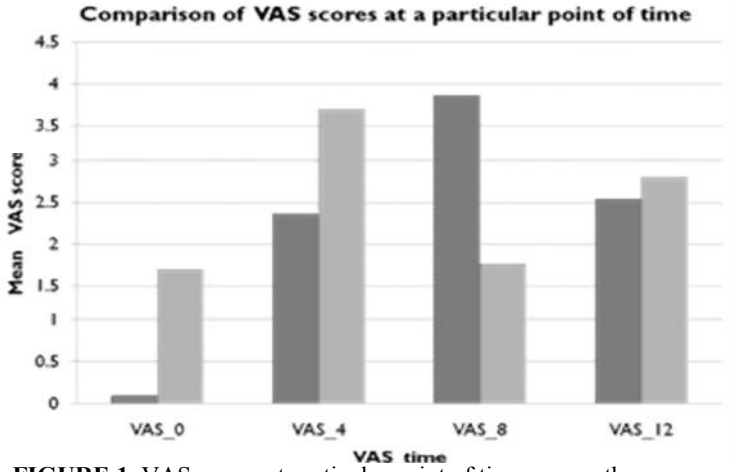

FIGURE 1. VAS scores at particular point of time among the groups

TABLE 4. Distribution of height of sensory block between both groups at specified point of time

	Group P n=50 Paracetamol				Group C n=50 Normal Saline				
	T2-T4	T5-T7	T8-T10	T11-T12	T2-T4	T5-T7	T8-T10	T11-T12	
10 Minutes	14	36	0	0	13	37	0	0	p=0.99
30 Minutes	26	24	0	0	18	32	0	0	p=0.114
1 Hour	10	30	10	0	20	04	24	2	p=0.002
2 Hours	05	35	10	0	0	13	37	2	p<0.001
3 Hours	03	25	22	0	0	06	35	09	p<0.001

TABLE 5. Comparison of time to first analgesic requirement among the groups

	Group P n=50 Paracetamol	Group C n=50 Normal Saline
Requirement of first rescue analgesic (hours) p<0.001	8.1±0.5	4.3±0.4

The mean time to first analgesic requirement was significantly more in Group P than in Group C ($p<0.001$). (Table-5).

Patient satisfaction were measured in point scale-excellent, good and Poor. Patient satisfaction was 90% excellent, 8% good, and 2% poor in paracetamol group whereas it was 70% excellent, 20% good and 10% poor in control group.

Adverse effects of paracetamol and placebo were quite comparable and include hypotension, bradycardia, dizziness, post-operative nausea and vomiting, urinary retention (Figure-2). Hypotension and bradycardia are normal physiological responses during spinal anesthesia because of sympathetic fibre block.

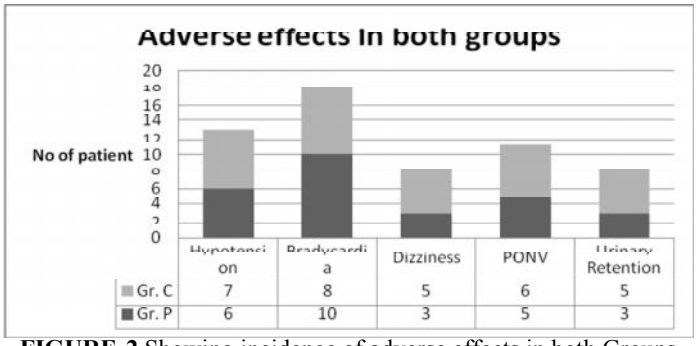

FIGURE-2 Showing incidence of adverse effects in both Groups

DISCUSSION

The study demonstrates that intravenous paracetamol infusion administration prior to spinal injection prolonged the duration of bupivacaine induced sensory blockade, delayed dermatomal regression, increased the time of first request of analgesic for post-operative pain relief.

Intravenous paracetamol (1 gm/100 ml) introduced in 2002 is a newer, easier and promising non opioid analgesic. Peak plasma concentration is achieved approximately 15 minutes after intravenous paracetamol. Maximal analgesic activity occurs 1-2 hours after peak plasma level. Hence intravenous paracetamol was administered 15 minutes before giving spinal injection. It is recommended to administer paracetamol slowly over 15 minutes, as rapid administration might produce flushing.

Synergistic interaction between paracetamol and local anesthetic has been observed in previous studies where paracetamol during IVRA with lidocaine decreased tourniquet pain, increased anesthesia quality, and decreased postoperative analgesic consumption [6, 7]. However, there are no clinical data regarding the association of intravenous paracetamol and intrathecal local anesthetic. Although this study showed that the intravenous paracetamol prolonged the duration of sensory block of bupivacaine spinal anesthesia and delayed the dermatomal regression of sensory block, the underlying mechanism of this effect remains unclear. Paracetamol has always been thought to have a strong central action, supported by the fact that paracetamol is found in significant concentration in the CSF after infusions in adults and in children [3]. Recently it was proposed that the analgesic effect of paracetamol might involve indirect activation of cannabinoid CB_1 receptor [5, 9]. In brain and spinal cord, paracetamol is metabolized to form N-arachidonylphenolamine (AM404). AM404 inhibits the cellular uptake of anndamide, an endocannabinoid, and is an agonist at the vanilloid receptor $TRPV_1$ that is believed to play a central role in nociception [4]. A recent study with IV paracetamol decreased propofol-induced injection pain, [23] demonstrated that paracetamol has some peripheral antinociceptive effects. In the CNS, paracetamol may act through several different pathways. First, it was shown that paracetamol attenuates prostaglandin synthesis through a weak cyclooxygenase inhibition[8,15] and there is evidence to suggest both peripheral[16] and central sites[17] of action that may involve inhibition of cyclooxygenase. Second, animal studies indicate that paracetamol antinociceptive action may also involve spinal nitric oxide pathways, which are associated with spinal glutamate N-methyl-D-aspartate receptor activation.[18] Finally; both animal and human experimental pain models consistently indicate that paracetamol acts at the CNS by serotonergic mechanisms.[10]. The analgesia observed following systemic administration of paracetamol results from a synergy between released supraspinal components, one of which is opioid-like. The independent contribution of the opioid-like component is small, so that there is minimal effect without paracetamol at the spinal site. The spinal cord component of paracetamol-induced antinociception, not an opioid-mediated effect, is activated when paracetamol enters the spinal site. The supra-spinal and peripheral actions of paracetamol may be the mechanism for prolongation of spinal sensory effect. In addition, compared with the prolongation of the sensory block, the duration of motor block was not affected by paracetamol. It could be explained that conduction of sensory nerve fibre might be more inhibited than motor nerve fiber at the same concentration of paracetamol.

It was demonstrated that intravenous paracetamol has a faster analgesic effect at early time points, a higher effectiveness and a longer analgesic effect than an equivalent paracetamol dosage compared to oral application.[12] Clinical studies have found that 1 g intravenous paracetamol employed alone is just as effective as 30 mg ketorolac, 75 mg diclofenac or 10 mg morphine.[13,14] Studies have also shown that intravenous paracetamol has an opioid-sparing effect and enhances patient satisfaction by reducing the opioid requirement.[15-17]

Varrasi and colleagues[21] assessed the relative morphine consumption in a combined analgesic regimen after gynecologic surgery with intravenous doses of propacetamol 2 g or ketorolac 30 mg. Patients were assessed regarding total dose of morphine, pain intensity and global efficacy. They established that total morphine requirements were not significantly different between the propacetamol (10.6±4.8 mg) and ketorolac (10.2±4.4 mg) groups. The evolution of pain intensity also showed similar patterns in the two groups.

Dahl and colleagues [22-24] evaluated the postoperative opioid-sparing effect of a pre-operative oral ibuprofen 800 mg and paracetamol 1000 mg in elective open hysterectomy patients that received test drugs orally 1 hour before the start of anesthesia. They found differences between the groups in postoperative pain measured by any variable or opioid consumption at any time and stated that

orally given ibuprofen or paracetamol does not have a postoperative analgesic or opioid-sparing effect. This may have been due to first-pass elimination of orally medicated drugs.

The success of postoperative pain management has an influence on patient satisfaction. There are many factors that define this success. Patient anxiety, communication with service nurses, and preoperative enlightenment are a few of these factors. In our study, we asked the patients if they were satisfied with the pain management during study period. We determined from the responses given that the gratification rate was high in paracetamol group.

IV paracetamol provided better analgesia as evident by decreased VAS Scores, reduction in analgesic consumption, increase in the time to request for analgesic and delaying dermatomal regression. It has a good margin of safety and better patient satisfaction. Thus our study not only brings to light this newer dimension pertaining to paracetamol but also demands attention from other workers so as to uncover facts more and more about this promising drug. However, as per our knowledge, no RCTs have been performed to venture into influence of intravenous paracetamol on spinal anesthesia; further studies are required in this respect.

REFERENCES

[1]. Dahl, J.L., Gordon, D., Ward, S., Skemp, M., Wochos, S., Schurr, M. (2003) Institutionalizing pain management: The postoperative pain management quality improvement Project.J Pain, 4:361-71.

[2]. Huang, N., Cunningham, F., Laurito, C.E., Chen, C. (2001) Can we do better with postoperative pain management. Am J Surg.,182:440-8.

[3]. Kumpulainen, E., Kokki, H., Halonen, T., Heikkinen, M., Savolainen, J., Laisalmi, M. (2007) Paracetamol penetrates readily into the cerebrospinal fluid of children after intravenous administration. Pediatrics, 119:766-71.

[4]. Hogestatt, E.D., Jonsson, B.A., Ermund, A., Andersson, D.A., Björk, H., Alexander, J.P. (2005) Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J Biol Chem., 280:31405-12

[5]. Alessandra Ottani, Sheila Leone, Maurizio Sandrini, Anna Ferrari and Alfio Bertolini (2006) .The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors.Eur J Pharmacol, 531(1-3):280-1.

[6]. Huseyin Sen,Yalcin Kulahci, Enis Bicerer, Sezai Ozkan, Guner Daglı, Alparslan Turan (2009) The Analgesic Effect of Paracetamol When Added to Lidocaine for Intravenous Regional Anesthesia.Anaesthesia Analgesia, 109:1327-1330.

[7]. Celik, M., Saricaoglu, F., Canbay, O., Dal, D., Uzumcigil, A., Leblebicioglu, G., Aypa,r U. (2009) The analgesic effect of paracetamol when added to lidocaine for intravenous regional anesthesia. Minerva, Nov 24.

[8]. Ayoub, S.S., Colville-Nash, P.R., Willoughby, D.A., Botting, R.M. (2006) The involvement of a cyclooxygenase 1 gene-derived protein in the antinociceptive action of paracetamol in mice. Eur J Pharmacol, 538:57–65.

[9]. Sandrini, M., Pini, L.A., Vitale, G. (2003) Differential involvement of central 5-HT1B and 5-HT3 receptor subtypes in the antinociceptive effect of paracetamol. Inflamm Res., 52:347–352

[10]. Pickering, G., Loriot, M.A., Libert, F., Eschalier, A., Beaune, P., Dubray, C. (2006) Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther., 79:371–378.

[11]. Bannwarth, B., Netter, P., Lapicque, F. (1992) Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol. Br J Clin Pharmacol., 34:79 –81.

[12]. Nakayama, Y., Omote, K., Kawamata, T., Namiki, A. (2004) Role of prostaglandin receptor subtype EP1 in prostaglandin E2-induced nociceptive transmission in the rat spinal dorsal horn. Brain Res.,1010:62 –68.

[13]. Allouia, A., Chassaing, C., Schmidt, J. (2002) Paracetamol exerts a spinal, tropisetron reversible, antinociceptive effect in an inflammatory pain model in rats.Eur J Pharmacol, 43(1-3):71-7.

[14]. Van der Marel, C.D., Anderson, B.J., Pluim, M.A., de Jong, T.H., Gonzalez, A., Tibboel, D. (2003) Acetaminophen in cerebrospinal fluid in children. Eur J Clin Pharmacol, 59 :297 –302.

[15]. Mitchell, J.A., Akarasereenont, P., Thiemermann, C., Flower, R.J., Vane, J.R. (1993) Selectivity of nonsteroidal anti-inflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci USA; 90:11693 –11697.

[16]. Colletti, A.E., Vogl, H.W., Rahe, T., Zambraski, E.J. (1999) Effects of acetaminophen and ibuprofen on renal function in anesthetized normal and sodium-depleted dogs. J Appl Physiol., 86 :592 –597.

[17]. Muth-Selbach, U.S., Tegeder, I., Brune, K., Geisslinger, G. (1999) Acetaminophen inhibits spinal prostaglandin E2 release after peripheral noxious stimulation. Anesthesiology, 91:231 –239.

[18]. Bjorkman, R. (1995) Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol: experimental studies in the rat. Acta Anaesthesiol Scand. 1995; 103(suppl):1 –44.

[19]. Anderson, B.J. (2008) Paracetamol (Acetaminophen): mechanisms of action. Paediatr Anaesth, 18:915–21.

[20]. Kumpulainen, E., Kokki, H., Halonen, T. (2007) Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. Pediatrics, 119(4) (4): 766-71.

[21]. Varrassi, G., Marinangeli, F., Agro, F. (1999) A double-blinded evaluation of proparacetamol versus ketorolac in combination with patient-controlled analgesia morphine: Analgesic efficiency and tolerability after gynecologic surgery. Anesth Analg 1999; 88: 611-16.

[22]. Dahl, V., Ernø, P.E., Ræder**,** J.C. (1997) No analgesic effect of ibuprofen or paracetamol *vs.* placebo for hysterectomies. European Journal of Pain; 1:31-35.

[23]. Borazan, Hale, Erdem, Tuba, B., Kececioglu, Melahat; Otelcioglu, Seref (2010) Prevention of pain on injection of propofol: a comparison of lidocaine with different doses of paracetamol. European Journal of Anesthesiology, 27:253-257.

[24]. Raffa, R.B., Stone, Jr, D.J., Tallarida, R.J. (2000) Discovery of 'self-synergistic spinal/supraspinal antinociception produced by Acetaminophen (Paracetamol). The Journal of Pharmacology and Experimental Therapeutics, 295:291-294.