Effect of Gabapentin on Postoperative Pain and Operation Complications A Randomized Placebo Controlled Trial

S Behdad[1], V Ayatollahi[1], A Tabatabaei Bafghi[2], M Dehghan Tezerjani[1], M Abrishamkar[1]

ABSTRACT

Objective: *Prevention and treatment of postoperative pain and operation complications such as nausea and vomiting are most important concerns in postoperative care. There are several mechanisms involved in postoperative pain. Gabapentin is a gamma aminobutyric acid analogue that is known as an anticonvulsant drug. This drug is tolerated well and has known effects on pain and anxiety. This study has compared the effect of gabapentin on postoperative pain, operation complications and haemodynamics.*

Subjects and Methods: *This randomized double blinded placebo controlled clinical trial was conducted on 61 patients divided randomly into two groups (30 as cases and 31 as controls). All patients had total abdominal hysterectomy. In the first group, the patients got 100 mg gabapentin in the night and 300 mg gabapentin orally (one capsule) two hours before surgery. The second group got one capsule of multivitamin orally. Then all patients were subjected to the same anaesthesia protocol and total abdominal hysterectomy. During the 24 hours after operation, the patients were assessed according to pain, nausea, vomiting, dizziness, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR) and morphine use at 1, 6, 12 and 24 hours.*

Results: *Mean age and weight of patients were 45.86 ± 4.06, 48.16 ± 4.48, 64.56 ± 13.29 and 68.8 ± 12.88 in the study population and control groups, respectively. Except in the first hour after operation (*p *= 0.02), there was no significant differences between the two groups in morphine use. There was no significant correlation between the groups according to postoperative complications and the haemodynamic parameters (PR, SBP and DBP).*

Conclusion: *Results show that gabapentin can decrease the need for morphine use in the first hour after operation only and has no significant effect on operation complications. Thus, we suggest gabapentin for pain management, and not to decrease opium use.*

Keywords: Abdominal hysterectomy, gabapentin, postoperative pain

Efecto de la Gabapentina en el Dolor Postoperatorio y Complicaciones de la Operación: un Ensayo Clínico, Aleatorio, *C*ontrolado con Placebo

S Behdad[1], V Ayatollahi[1], A Tabatabaei Bafghi[2], M Dehghan Tezerjani[1], M Abrishamkar[1]

RESUMEN

Objetivo: *La prevención y tratamiento de dolor postoperatorio y las complicaciones de la operación – tales como la náusea y el vómito – son problemas de suma importancia en el cuidado postoperatorio. Hay varios mecanismos implicados en el dolor postoperatorio. La gabapentina es un análogo del ácido gamma-aminobutírico, conocido como un medicamento anticonvulsivo. Este medicamento es bien tolerado, y tiene efectos conocidos sobre el dolor y la ansiedad. El presente estudio compara el efecto de la gabapentina sobre el dolor postoperatorio, las complicaciones de la operación, y la hemodinámica.*

Sujetos y Métodos: *Este ensayo clínico, aleatorio, doble ciego y controlado con placebo, se llevó a cabo con 61 pacientes divididos aleatoriamente en dos grupos (30 como casos y 31 como control).*

From: [1]Department of Anaesthesiology, and [2]Department of Gynaecology, Shahid Sadoughi University of Medical Sciences, Iran.

Correspondence: Dr V Ayatollahi, Department of Anaesthesiology, Shahid Sadoughi Hospital, Ibn sina Boulevard, Yazd, Iran. E-mail: ayati.vida@yahoo.com

Todas las pacientes tuvieron histerectomía abdominal total. En el primer grupo, las pacientes recibieron vía oral 100 mg de gabapentina por la noche y 300 mg de gabapentina (una cápsula) dos horas antes de la cirugía. El segundo grupo recibió una cápsula de multivitaminas por vía oral. Luego, todas las pacientes fueron sometidas al mismo protocolo de anestesia e histerectomía abdominal total. Durante las 24 horas después de la operación, las pacientes fueron evaluadas en relación con dolores, náusea, vómitos, vértigo, presión sanguínea sistólica (PSS), presión sanguínea diastólica (PSD), frecuencia de pulso (FP), y el uso de morfina a la 1, 6, 12 y 24 horas.

Resultados: *La edad promedio y el peso de las pacientes fue 45.86 ± 4.06, 48.16 ± 4.48, 64.56 ± 13.29 y 68.8 ± 12.88 en la población de estudio y los grupos de control, respectivamente. Excepto en la primera hora tras la operación (*p = *0.02), no hubo ninguna diferencia significativa entre los dos grupos en cuanto al uso de morfina. No hubo correlación significativa alguna entre los grupos sobre la base de las complicaciones postoperatorias y los parámetros hemodinámicos (FP, PSS, y PSD).*

Conclusión: *Los resultados muestran que la gabapentina sólo puede disminuir la necesidad del uso de morfina en la primera hora tras la operación, y no tiene efectos significativos en las complicaciones de la operación. Por lo tanto, se sugiere el uso de la gabapentina para el tratamiento del dolor, pero no para reducir el uso del opio.*

Palabras claves: histerectomía abdominal, gabapentina, dolor postoperatorio

West Indian Med J 2012; 61 (2): 129

INTRODUCTION

Prevention and treatment of postoperative pain and operation complications such as nausea and vomiting are major concerns in postoperative care, and affect rapid ambulation and patient satisfaction with surgery. Opioid derivatives are the most popular drugs used for this purpose, so current research in this field are focussed on finding new alternative drugs or drugs that can be combined with opioid to reduce the need for its use (1).

Hysterectomy is one of the most common types of surgery. Hysterectomy is still the only definitive treatment of dysfunctional uterine bleeding (DUB) and, compared with most other alternative therapies, has acceptable satisfaction. In the majority of cases, hysterectomy is performed through the abdomen, although in many cases, vaginal surgery is considered less complicated than abdominal hysterectomy (2). Ordinarily, abdominal hysterectomy is done through an incision called a Pfannenstiel incision which causes considerable pain that often needs opioid use within the first 24–48 hours after surgery (3). Administration of morphine is associated with complications such as decreased intestinal motility, nausea and vomiting (4).

Different mechanisms are involved in postoperative pain, such as sensitivity of nociceptives (afferent nerve activity after nerve stimulation in the peripheral and central neurons that can cause tissue destruction). The process is created by pain receivers (nociceptor) and is sensitive to mechanical, chemical and heat stimulation and generates nerve messages throughout the brain and spinal cord, leading to pain (5). This process will be determined by mechanical pain hyperstimulation at the intact skin surrounding the operation wound (6). Central neurons sensitivity probably is involved in postoperative pain so some researchers think analgesic drugs in this process can be effective. These drugs can prevent development of pain stimulation in the central nervous system (CNS) and cause analgesic effects beyond their pharmacologic effects (7).

Gabapentin is a gamma-aminobutyric acid analogue that was originally an anticonvulsant drug (8). It is used for neuropathic pains, diabetic neuropathy, post herpetic pain and reflex sympathetic dystrophy (8 – 10). It is an analgesic drug that can be affected directly by interaction with nociception in the CNS (9). This drug has good compliance and anti-anxiety effects (9). Its half life is 5–9 hours (11).

There are several studies about the possible effect of gabapentin on postoperative pain. But there are few studies on its effect on surgery complications and haemodynamic changes. This study compares the effect of gabapentin with placebo on postoperative pain and haemodynamic parameters in patients who underwent abdominal hysterectomy.

SUBJECTS AND METHOD

After approval from the University institutional ethics committee, this double blinded placebo controlled randomized clinical trial was conducted on 61 patients who were for total abdominal hysterectomy under general anaesthesia. The study was registered in the Iranian registry of clinical trials (http://irct.ir); IRCT138810122963N1. Patients were randomly assigned to one of the two groups (31 patients in control and 30 in study population). Patients had to be at least 20 years old and over 40 kg of weight. All patients with a history of sensitivity to opioids, asthma, renal failure, peptic ulcer, mental diseases, cardiovascular diseases, body mass index (BMI) more than 35 and previous surgery with more than 2.5 hours duration were excluded from the study.

Patients in the study population got 100 mg gabapentin in the night and 300 mg gabapentin (one capsule) two hours

before surgery. The drugs were given by the resident in gynaecology. In group 2, patients got one capsule of multivitamin two hours before surgery. Before prescription of the drug, the resident explained the process of the study, the type of drug and its possible complications and a signed consent was obtained from the patient. All patients underwent the same anaesthesia protocol. All patients were premedicated with midazolam 2 mg, 30 minutes before the operation. Induction of anaesthesia was with propofol (2 mg/kg IV) and after administration of atracurium (0.5 mg/kg IV), laryngoscopy and intubation were performed. Maintenance of anaesthesia was with infusion of propofol (100 µg/kg/min) and O2-N2O (50%–50%). Fentanyl (2 µg/kg IV) was administered two minutes before laryngoscopy and intubation and the patients received 5 mg morphine (IV) during the operation. At the end of the operation, residual neuromuscular blockade was reversed with neostigmine (0.04 mg/kg IV) and atropine (0.02 mg/kg IV). After tracheal extubation and awakening from anaesthesia, patients were transferred to the post anaesthesia care unit (PACU).

During the first 24 hours after surgery, at 1, 6, 12, and 24 hours, patients were evaluated for pain, and need for opioid. Vital signs (pulse rate (PR), systolic blood pressure (SBP) and diastolic blood pressure (DBP)) and postoperative complications such as dizziness, nausea and vomiting were also assessed. Evaluation and documentation of data were done by a researcher who was not aware of the patient's study group.

Pain was assessed according to the Pain Assessment Ruler (PAR). In this study, pain was graded between 0–10 levels (no pain to severe pain). Evaluation on this scale was subjective and was done by a researcher in our study. All data were transferred to SPSS software and analysed by Chi-square, ANOVA and Mann-Witney.

RESULTS

A total of 73 patients were selected for the study; 12 patients did not satisfy the inclusion criteria and were excluded. Sixty-one patients were included finally, with 30 patients in the study population and 31 in the control group.

Mean age was 45.86 ± 4.06 years in the study population and 48.16 ± 4.48 years in the control group. Mean weight for the study population was 64.56 ± 13.29 kg and 68.8 ± 12.88 kg for the control group. In comparing the pain scores, there was a significant difference between the two groups at all evaluated times ($p < 0.001$) and pain in the study population was lower than in the control (Table 1). In comparing of the vital signs of patients in Mann-Witney analysis, there was no significant difference between the two groups. Detailed data are shown in Table 2.

Table 1: Mean ± SD of pain score for case and control groups

Time of measurement (hours)	**1**	**6**	**12**	**24**
Group				
case	3.8 ± 0.93	3.8 ± 0.96	3.46 ± 1.07	2.53 ± 0.5
control	7.72 ± 1.1	6.62 ± 1.37	5.59 ± 1.51	4.27 ± 1.42

Chi-square $p < 0.001$

Table 2: Mean ± SD for pulse rate (PR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) and related p values (Mann-Witney)

Time of measurement (hours)		**1**	**6**	**12**	**24**
Group					
PR	Case	83.12 ± 12	81.43 ± 5.07	80.53 ± 4.02	79.23 ± 6.57
	control	82.83 ± 6.41	82.7 ± 6.38	82.29 ± 5.43	82.67 ± 4.31
		$p = 0.135$	$p = 0.633$	$p = 0.394$	$p = 0.062$
SBP	Case	115.9 ± 11.14	114 ± 10.45	111.5 ± 6.45	111.8 ± 5.33
	control	120.9 ± 19.52	115.1 ± 10.2	115.1 ± 9.95	116.7 ± 11.36
		$p = 0.315$	$p = 0.623$	$p = 0.163$	$p = 0.65$
DBP	Case	74.56 ± 7.92	71.2 ± 6	68.83 ± 5.82	69.83 ± 4.44
	control	74 ± 8.04	70.8 ± 5.49	70.32 ± 4.46	69.51 ± 4.89
		$p = 0.67$	$p = 0.99$	$p = 0.312$	$p = 0.912$

In comparison of the two groups, according to need for opioid use during the first 24 hours after surgery, except for the first hour ($p = 0.02$), there were no significant differences between the two groups. Table 3 shows the extent of opioid use in patients and related *p*-values.

DISCUSSION

Sensitization of central neurons probably plays a key role in postoperative pain and some researchers suggested analgesics for management of this type of pain. These drugs can prevent spreading of stimulation in the CNS and can give analgesia beyond their pharmacologic effect.

Table 3: Opioid use in two groups at different times (Chi-square)

Time of measurement (hours)	**1**		**6**		**12**		**24**	
Group								
	no	yes	no	yes	no	yes	no	yes
	25	5	17	13	27	3	28	2
Case	83.3%	16.7%	56.7%	43.3%	90%	10%	93.3%	6.7%
	16	15	17	14	31	0	29	2
Control	51.6%	49.4%	54.8%	45.2%	100%	0%	93.5%	6.5%
p	0.02		0.18		0.11		**0.51**	

Also there were no significant discrepancies between the two groups in relation to dizziness, nausea and vomiting as postoperative complications (Table 4).

Many studies showed that gabapentin decreases postoperative pain, but the doses of gabapentin and type of surgery were different. Because gabapentin has dose-dependent

Table 4: Comparison of two groups in dizziness, nausea and vomiting (Chi-square)

Time of measurement (hours)		**1**		**6**		**12**		**24**	
Group									
		no	yes	no	yes	no	yes	no	yes
		30	0	26	4	27	3	28	2
	Case	100%	0%	86.7%	13.3%	90%	10%	93.3%	6.7%
Dizziness		31	0	30	1	31	0	31	0
	Control	100%	0%	96.8%	3.2%	1005	0%	100%	0%
		$p = 1$		$p = 0.16$		$p = 0.11$		$p = 0.23$	
		25	5	14	16	22	8	29	1
	Case	83.3%	16.7%	46.7%	53.3%	73.3%	26.7%	96.7%	3.3%
Nausea		26	5	18	13	27	4	31	0
	Control	83.9%	16.1%	58.1%	41.9%	87.1%	12.9%	100%	0%
		$p = 0.61$		$p = 0.26$		$p = 0.15$		$p = 0.49$	
		25	5	13	15	18	12	28	3
	Case	83.3%	16.7%	43.3%	9.7%	56.7%	60%	40%	93.3%	9.7%
Vomiting		24	7	18	13	21	10	28	3
	Control	77.4%	22.6%	58.1%	41.9%	67.7%	32.3%	90.3%	9.7%
		$p = 0.39$		$p = 0.18$		$p = 0.35$		$p = 0.51$	

side effects such as dizziness, nausea and vomiting, we decided to choose a relatively effective and tolerable dose. So we used 100 mg gabapentin orally at night and 300 mg gabapentin two hours before total abdominal hysterectomy and the results showed gabapentin at this dose can decrease pain during the first postoperative day without significant side effects and less need for opioid use during the first hour after surgery.

In a study conducted in France, results showed that 1200 mg of gabapentin before knee surgery can decrease pain and the need for opioid use but not until 48 hours after surgery (12). In research in Iran, gabapentin was used in two 300 mg doses at night and two hours before surgery. Results showed that gabapentin could reduce pain and the need for opioid use until 48 hours after hysterectomy but had no effect on nausea and vomiting (13). In another study done by Montazeri *et al,* results showed that 300 mg gabapentin before lower extremity surgery can lower pain and opioid use for 24 hours (14). Turan *et al* concluded that gabapentin and rofecoxib both can have an effect on postoperative pain similarly although they suggested the combination of these drugs is more effective (15). There are similar results in other studies (16–20). However, the results of these studies are not concordant with ours. While these studies demonstrated that gabapentin decreased the needs for opioid, they did not mention whether their opioid prescription was blinded or not. In our study, opioid prescription was blinded. It is doubtless that analgesics can affect the CNS beyond their pharmacologic effects (pre-emptive analgesia) and these studies referred to this longterm action despite the 5–9 hours half life of gabapentin to this effect. In the present study, pain was lower in the gabapentin group; on the other hand, except in the first hour after surgery, there was no significant difference in opioid use between the two groups. Both groups got similar doses of opioid except in the first hour; continuity in lowering pain in the gabapentin group can be attributable to opioid and its possible synergistic and cumulative effect on gabapentin, and not just gabapentin alone.

In a study done by Iranian researchers after administration of 600 mg gabapentin to patients who were candidates for open cholecystectomy, they concluded that gabapentin can decrease pain and also nausea and vomiting (21). These results were repeated in another study in India (22). These two studies suggested anti-emetic effects for gabapentin. These studies involved cholecystectomy, a surgery with high incidence of nausea and vomiting (23); it is possible that this high incidence helped the anti-emetic effects of gabapentin to become more apparent.

Bartholdy *et al,* after administration of 1200 mg of gabapentin and comparison of it with placebo, concluded that gabapentin had no effect on pain, nausea and vomiting after tubal ligation (24).

In a systematic review done in Denmark in 2007 (25), results of 23 studies were re-analysed by meta-analysis. This study concluded that gabapentin can decrease postoperative pain in the early hours after surgery rather than later. It could not reduce dizziness and vomiting but decreased nausea. These studies had low sample size and power. They also mentioned the low extent of pain in hysterectomy patients in the first hour after surgery and this was similar to our study. It may be that the natural decrease in pain over time influenced the significance of the pain difference in later hours. The results of this reliable study are concordant with our study.

In another systematic review in 2010 (26), results showed that 250 mg gabapentin had no clinical effects. Our study used 300 mg of gabapentin and it seemed that at this dose, gabapentin was more effective.

There was no previous study on vital signs. In our study, we concluded that there was no significant relation between groups with regard to vital signs. Mean ± SDs in our groups were within normal ranges and almost all of our cases were under 50 years of age and had no underlying cardiovascular diseases. It is possible that if this drug was tried in older patients and those with cardiovascular diseases, a better understanding of this aspect of gabapentin could be attained.

Finally, it seems that gabapentin can decrease postoperative pain but has no long term effect on reducing the need for opioid use. It may be more effective for better pain management than for decreasing opioid use.

ACKNOWLEDGEMENT

This article was extracted from a thesis which was in part fulfilment of a general medicine degree. It was supervised and supported by the Faculty of Medicine of Shahid Sadoughi University of Medical Sciences.

REFERENCES

1. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. Lancet 2003; **362:** 1921–8.
2. Manyonda IT, Hadoura E. Total abdominal hysterectomy. In: O'Donovan PJ, Miller CE, eds. Modern Management of Abnormal Uterine Bleeding, First Edition. London: Informa Healthcare; 2008: 267–79.
3. Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. British Journal of Anaesthesia 2003; **90:** 746–9.
4. Ng A, Parker J, Toogood L, Cotton BR, Smith G. Does the opioid-sparing effects of rectal diclofenac following total abdominal hysterectomy benefit the patient? Br J Anaesth 2002; **88:** 714–6.
5. Woolf CJ, Chong MS. Preemptive analgesia: treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993; **77:** 362–79.
6. Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB. Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. Pain 2000; **86:** 19–24.
7. McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-d- aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004; **98:** 1385–400.
8. Rose MS, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002; **57:** 451–62.

9. Rosner H, Rubin L, Kestenbaum A. Gabapentin adjunctive therapy in neuropathic pain states. Clin J Pain 1996; **12:** 56–8.
10. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomised controlled trial. JAMA 1998; **280:** 1831–6.
11. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002; **97:** 560–4.
12. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005; **100:** 1394–9.
13. Ghafari MH, Akrami M, Nouralishiri B, Sadegh A. Preoperative gabapentin or clonidin decreases postoperative pain and morphine consumption after abdominal hysterectomy. Research Journal of Biological Sciences 2009; **4:** 458–63.
14. Montazeri K, Kashefi P, Honarmand A. Pre-emptive gabapentin significantly reduces Postoperative pain and morphine demand following lower extremity orthopaedic surgery. Singapore Med J 2007; **48:** 748–51.
15. Turan A, White PF, Karamanlioglu B, Memis D, Tasdogan M, Pamukçu Z et al. Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesth Analg 2006; **102:** 175–81.
16. Turan A, Karamanlioğlu B, Memiş D, Usar P, Pamukçu Z, Türe M. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg 2004; **98:** 1370–3.
17. Ucak A, Onan B, Sen H, Selcuk I, Turan A, Yilmaz AT. The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2011; **25:** 824–9.
18. Parikh HG, Dash SK, Upasani CB. Study of the effect of oral gabapentin used as preemptive analgesia to attenuate postoperative pain in patients undergoing abdominal surgery under general anesthesia. Saudi J Anaesth 2010; **4:** 137–41.
19. Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. Anesth Analg 2011; **112:** 167–73
20. Sen H, Sizlan A, Yanarates O, Emirkadi H, Ozkan S, Dagli G et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesth Analg 2009; **109:** 1645–50.
21. Khademi S, Ghaffarpasand F, Heiran HR, Asefi A. Effects of preoperative gabapentin on postoperative nausea and vomiting after open cholecystectomy: a prospective randomized double-blind placebo-controlled study. Med Princ Pract 2010; **19:** 57–60.
22. Srivastava U, Kumar A, Saxena S, Mishra AR, Saraswat N, Mishra S. Effect of preoperative gabapentin on postoperative pain and tramadol consumption after minilap open cholecystectomy: a randomized double-blind, placebo-controlled trial. Eur J Anaesthesiol 2010; **27:** 331–5.
23. Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth 1999; **83:** 772–5.
24. Bartholdy J, Hilsted KL, Hjortsoe NC, Engbaek J, Dahl JB. Effect of gabapentin on morphine demand and pain after laparoscopic sterilization using Filshie clips. A double blind randomized clinical trial. BMC Anesthesiol 2006; **6:** 12.
25. Mathiesen O, Møiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiol 2007; **7:** 6.
26. Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. Cochrane Database Syst Rev 2010; CD008183.