DISCUSSION

Though, postoperative pain has been generally reduced, with advent of laparoscopy as alternative to traditional open surgery, yet often, it can still peak with varying incidence and intensities, especially during the early postoperative period.[133]

Opiates when used, did succeeded to control such pain but at the expense of increased side effects such as respiratory depression, drowsiness and sedation, postoperative nausea and vomiting (PONV), pruritus, urinary retention, ileus, and constipation, that can delay hospital discharge and contribute to unanticipated admission especially in obese patients. Intraoperative use of large bolus doses or continuous infusions of short acting potent opioid analgesics may actually increase postoperative pain as a result of their rapid elimination and/or development of acute tolerance. That is why the search for an effective and safe opioid-sparing pain-control therapy to be added in a setting of preemptive and multimodal analgesia has been probed in many current researches.[98]

Therefore, anesthesiologists and surgeons are increasingly turning to non-opioid analgesic techniques as adjuvants for managing pain during perioperative period to minimize adverse effects of opioid medications. [98]

In such a context, this study, aimed at evaluating the efficacy of preoperative single dose of gabapentin on immediate postoperative pain (followed for up to 24 hours postoperative) and analgesic consumption (nalbuphine being the chosen drug) in patients undergoing laparoscopic sleeve gastrectomy.

This study was carried out at Alexandria University main hospital, on 50 adult patients of ASA physical status I and II undergoing sleeve gastrectomy and planned for at least 24 h postoperative hospital stay. Patients were randomized into two groups:

For group I (25 patients), a single 1 g dose of intravenous (IV) paracetamol was given 30 minutes before induction of anaesthesia. While for group II (25 patients), a single 1g dose of IV paracetamol was given 30 minutes before induction of anaesthesia plus 1.2 g of oral gabapentin given 2 h before induction of anaesthesia.

Results of the present study, showed no substantial difference among the studied groups with regards to the demographic data [age, sex, duration of surgery and BMI]. This indicates that the afore-mentioned variables would have least influence on the assessed parameters when comparing effects of gabapentin to controls, on post-operative pain, in the current laparoscopic sleeve gastrectomy study.

Throughout the operative period, the hemodynamic profile was also checked when gabapentin was used, as it partially reflects its pain controlling ability and can index its intra-operative safety potentiality.

As regard HR in the present study, it was significantly decreased in gabapentin group compared to controls at the immediate preinduction time, after intubation, during the whole intraoperative period, after extubation and during the postoperative period except at 12 h postoperatively where this decrease was insignificant.

In agreement with the results of the present study, **Neogi et al**[134] used oral gabapentin 900 mg 2h before laparoscopic cholecystectomy versus placebo in 60 adult normotensive patients. They found a significant lower HR in gabapentin group after endotracheal intubation, before pneumoperitoneum (PP), 15 and 30 min after PP and 10 min after release of PP and after extubation.[134]

These favourable haemodynamics were attributed to the possible voltage gated Ca^{+2} channel blocking mechanism. Although, they found HR insignificantly changed at the preinduction time, it was kept at a lower range in gabapentin group.[134]

Also, in a study carried out by **Bharti et al,**[135] 40 adult females scheduled for total mastectomy for breast cancer were included. Patients were randomly allocated to receive oral gabapentin 600 mg or placebo 2h before surgery. They found that patients in gabapentin group had lower HR at preinduction time and after intubation compared to placebo.[135] This was explained by the attenuated preoperative anxiety and haemodynamic response to laryngoscopy and tracheal intubation exerted by gabapentin.[135] Also, the relation between anxiety and increased HR was previously confirmed in a separate study.[136]

Also, in a study of **Butt et al,**[137] who carried out a randomized double blind placebo controlled study in patients undergoing mastectomy. They found that oral gabapentin 1200 mg given 1 h prior to surgery significantly decreased HR during the intraoperative and postoperative periods that was explained by reduced incidence of pain and significant analgesic effect exerted by gabapentin.[137]

On studying the effect of two different doses of gabapentin on haemodynamic response to laryngoscopy and intubation, **Bafna et al**,[138] randomly divided 90 adult normotensive patients requiring endotracheal intubation for elective surgery into 3 groups. Group I received oral placebo, Group II received 600 mg of oral gabapentin and Group III received 1g of oral gabapentin, 1 h prior to surgery. They concluded that oral gabapentin resulted in significant decrease in HR in the first ten minutes after intubation. This effect was found to be dose dependent.[138]

Bafna et al proposed that attenuated HR by gabapentin after intubation may be due to inhibition of membrane voltage gated Ca^{+2} channels, thus acting in a manner similar to calcium channel blockers. Another proposed mechanism was the decreased synthesis of neurotransmitter glutamate. Limitations of the study were that they did not measure stress mediators such as endogenous plasma catecholamines or cortisone, and they did not score sedation.[138] However, **Todd et al**,[139] concluded that Gabapentin inhibits catecholamine release from adrenal chromaffin cells which plays a potential contributor to some of its beneficial perioperative effects and might contribute to modulation of the sympathoadrenal stress response. This was independent from effects on Ca^{2+} entry, perhaps through disruption of the exocytotic machinery or vesicular trafficking events (calcium was less effective in triggering vesicle fusion).

Also, **Ali et al**[140] concluded that single dose of gabapentin 800mg, given 2 h before eye surgery using endotracheal intubation, can attenuate tachycardic response to laryngoscopy and intubation; while single dose of gabapentin 1.2 g given at the same time keeps HR below baseline values; also both doses of gabapentin succeeded to reduce HR during the first 10 minutes after intubation compared with control group. This was

explained by binding of gabapentin to the $\alpha 2$-$\gamma 1$ subunit of voltage dependent Ca channels, acting in a way similar to calcium channel blockers.[140]

Also, **Memis et al**[141] compared the effect of 2 different doses of gabapentin on haemodynamic response of laryngoscopy and intubation. They concluded that gabapentin 800 mg given 1 h before operation, blunted HR increase in first 10 minutes after endotracheal intubation compared to 400mg group or placebo group.

Also, **Shrestha et al**[142] studied 75 adult patients undergoing laparoscopic cholecystectomy who were randomized to orally receive 600 mg gabapentin, 150 mcg clonidine or placebo 1 h prior to induction of anesthesia. Serum glucose and cortisol were sampled before and 10 minutes after pneumoperitoneum (PP). They concluded that oral clonidine or gabapentin premedication offers more haemodynamic stability in laparoscopic cholecystectomy. When serum cortisol was taken as a stress marker, gabapentin group exhibited significant attenuation of stress of PP.[142]

Favourable haemodynamic parameters with gabapentin are attributed to preoperative anxiolytic effect, less sympathoadrenal stress response to surgery, inhibition of membrane voltage gated Ca^{+2} channels and favourable postoperative pain scores and sedation exerted by gabapentin.[138-140, 142]

In contrast with the results of present study, **Fassoulaki et al**[143] randomly divided 46 patients undergoing abdominal hysterectomy for benign disease to receive gabapentin 1.6 g or placebo capsules at 6 h intervals starting the day (noon) before surgery. They concluded that gabapentin did not attenuate tachycardia associated with laryngoscopy and tracheal intubation. It was assumed that tachycardia resulting from intubation may have been attenuated by propofol in both groups covering such a possible effect of gabapentin on the HR. Beside producing bradycardia, propofol produces hypotension, which may compensate in part the cardiovascular changes attributable to laryngoscopy and tracheal intubation.[143]

Also, **Bahandari et al**[144] studied the effect of 600mg oral gabapentin versus placebo on 40 patients scheduled for laparoscopic cholecystectomy . They found no effect on HR which was explained by the possible low dose of gabapentin compared to doses used in other studies.[144]

Also, **Khezri et al**[145] compared the effect of melatonin and gabapentin on patients of cataract surgery. Patients were randomly allocated to one of three groups each with 40 patients to receive melatonin 6 mg, gabapentin 600 mg or placebo 90 min before reaching the operating room. Retrobulbar block (RBB) was done by an ophthalmologist. The comparison of hemodynamic variables changes during the RBB placement and surgery did not reveal any statistically significant difference between the three groups.[145]

The disagreement of **Khezri et al**[145] may be related to physiology of elderly patients undergoing cataract surgery who are known to under-report their pain and stress due to cognitive dysfunction and depression. Also, it may be related to low pain scores obtained after performance of RBB.[145]

Also, in a study carried out by **Turan et al**,[146] 1200 mg of gabapentin administered 1 h before total abdominal hystrectomy had no significant effect on HR at all the measured postoperative 24 h; however it was kept at a lower range in gabapentin group.[146]

As regard MAP in the present study, it was significantly decreased in gabapentin group after intubation, extubation and during all the postoperative period. Although, there was no significant change during the preinduction and intraoperative periods, MAP was maintained at a lower range at these times.

In agreement with the results of present study, **Bharti et al**[135] found lower MAP at preinduction time in comparison with the control group. This was explained by the attenuated preoperative anxiety exerted by gabapentin.[135]

The result of present study also agrees with the previously described study of **Neogi et al** [134] who found significant lower MAP after intubation, during pneumoperitoneum and after extubation. They found no significant MAP readings at preinduction period; however, these readings were at a lower range in gabapentin group that agrees with the results at preinduction time of present study.[134]

Also, **Kavitha et al**[147] compared effects of gabapentin premedication to diazepam in 56 elderly patients undergoing elective intraocular surgery. There was a significant fall in MAP in the gabapentin group compared with the control group during the intraoperative period. Similarly, **Kaya et al**[148] used 800mg oral gabapentin 2 h before surgery with endotracheal tube and they concluded that gabapentin effectively suppresses the increase in MAP secondary to intubation.

Also, **Soltanzadeh et al**[149] had randomized patients scheduled for elective surgery under general anesthesia and endotracheal intubation to receive placebo or 900 mg oral gabapentin 2h before surgery. They found that MAP at 1, 3 and 5 minutes after laryngoscopy and tracheal intubation in the gabapentin group were significantly lower than placebo. It acts by decreasing the synthesis of glutamate and by binding to α2δ subunit of voltage dependent calcium channel. Action similar to calcium channel blockers may be responsible for blunting hemodynamic response to laryngoscopy and intubation.[149]

Also, in the previously described study of **Butt et al**,[137] they found MAP significantly lower in gabapentin group during the intraoperative period. These favourable haemodynamics were explained by alleviated hemodynamic response to noxious stimuli and pneumoperitoneum exerted by gabapentin.[137]

Also, **Misra et al**[150] studied 47 adult patients, scheduled for elective craniotomy for intracranial tumor surgery. Patients were randomly divided into 3 groups; L (oral placebo plus 2% lidocaine infiltration at pin sites; n=12), G (oral gabapentin 900 mg plus normal saline infiltration; n=21) and GL (oral gabapentin 900 mg plus 2% lidocaine infiltration; n=14). The oral medications were administered 2 h before induction of anesthesia. They concluded that gabapentin with lidocaine scalp infiltration abolished the hemodynamic response after skull pin insertion. Premedication with gabapentin alone significantly attenuated the SBP and MAP; however, HR responses were more variable.[150]

In contrast to the results of present study, **Turan et al,**[146] found that 1200 mg of oral gabapentin given 2 h before hysterectomy, has no significant effect on MAP during the

whole postoperative 24 h; however these parameters were kept at a lower range in gabapentin group.[146]

As regard O_2 saturation in the present study, it was insignificantly changed on comparing both groups, either preoperatively, intraoperatively or postoperatively.

In agreement with the results of present study, **Gilron et al** [151] had evaluated efficacy of a gabapentin–rofecoxib combination following hysterectomy in 110 patients. In addition to PCA morphine, patients received either placebo, gabapentin (1.8 g/day), rofecoxib (50 mg/day) or a gabapentin–rofecoxib combination starting 1 h pre-operatively for 72 h. they found no significant difference between the studied groups as regard O_2 requirements or saturation.[151]

As regard VAS in the present study, it was significantly decreased among patients of gabapentin group on both static and dynamic pain assessment, however; this decrease was more obvious with dynamic pain.

In agreement with the results of present study, **Srivastava et al**[152] had randomized 120 adult patients to orally receive 600 mg of gabapentin or a matched placebo, 2 h before minilap open cholecystectomy in a double-blind manner.VAS was significantly lower on first postoperative day at all times of observation both at rest and at movement in gabapentin group compared to placebo group.[152]

Also, **Yu et al**,[153] studied the effect of preemptive gabapentin and pregabalin in management of postoperative lumbar spinal surgery pain. Seven trials were included in that study. The pooled results from meta-analysis demonstrated that compared with placebo, both gabapentin and pregabalin could significantly reduce the postoperative narcotic consumption and were found to be efficacious in the management of postoperative pain at all time points during the first day after surgery.[153]

Also, in another systematic review consisted of 22 randomized controlled trials, **Tiippana et al,**[154] found that pain relief was better in the gabapentin groups compared with the control groups. The opioid-sparing effect during the first 24 h after a single dose of gabapentin 300–1200 mg, administered 1–2 h preoperatively, ranged from 20% to 62%. The combined effect of a single dose of gabapentin was a reduction of opioid consumption equivalent to 30 ± 4 mg of morphine during the first 24 h after surgery that was not significantly dependent on the gabapentin dose.[154]

Also, **Najafi Anaraki et al**[155] studied 78 primiparous women who were scheduled for elective cesarean delivery. Patients received 12.5 mg of heavy bupivacaine 0.5 % plus (10 micg of fentanyl intrathecally or 300 mg of oral gabapentin 2 h before surgery). They found that mean postoperative VAS in the fentanyl group was significantly higher than the gabapentin group. They concluded that preemptive use of gabapentin is a safe and effective way to reduce postoperative pain and morphine consumption after cesarean surgery.[155]

Also, **Rorarius et al**[156] compared the effect of 1200 mg of oral gabapentin versus 15 mg of oxazepam (active placebo) given 2.5 h prior to induction of anaesthesia in patients undergoing elective vaginal hysterectomy in an active placebo-controlled, double blind, randomized study. They found that VAS was significantly higher in the active

placebo group compared to the gabapentin-treated patients during the first postoperative 2 h.[156]

Also, in a study carried out by **Kosucu et al,**[157] sixty adult patients undergoing segmentectomy were randomly divided into two groups to orally receive pre-emptive gabapentin 1.2 g or placebo. They found that the time to first analgesic requirement was delayed and total morphine and additional analgesic consumptions were less in gabapentin group. Moreover, gabapentin reduced persistent post-thoracotomy pain during the first year.[157]

In contrast to the results of present study, **Zakkar et al**[158] performed a literature search and identified five papers with the best evidence regarding the use of gabapentin to reduce the incidence of pain after thoracic surgery. They concluded that there is no evidence to support the role of a single preoperative oral dose of gabapentin in reducing pain scores or opioid consumption after thoracic surgery. However; they needed to validate the efficacy of multiple dosing regimens through more robust randomized control studies.[158]

Also, **Radhakrishnan et al**[159] randomly divided 60 adult patients scheduled for elective lumbar laminectomy or discectomy to receive either gabapentin 800mg (in two equally divided doses) or placebo. In the postoperative period, the VAS for pain at 0, 2, 4, 6, and 8 h was not significantly different between the two groups. Total morphine consumption and side effects were similar in the two groups. They concluded that gabapentin did not decrease the morphine requirement or morphine side effects in the immediate postoperative period following lumbar laminectomy and discectomy.[159]

Also, **Paul et al,**[160] studied the effect of gabapentin in patients undergoing primary total knee arthroplasty compared to placebo. All subjects received oral acetaminophen 1g and oral ketorolac 15 mg preoperatively. Postoperatively, subjects received acetaminophen 1g and ketorolac 15 mg orally every 6 h and morphine PCA. They concluded that oral gabapentin 600 mg given preoperatively followed by 200 mg given orally every 8 h for 2 days has no effect on pain scores, postoperative morphine consumption, patient satisfaction, or length of hospital stay.[160]

Also, **Siddiqui et al**[161] examined the effect of gabapentin in patients with IBD undergoing major bowel surgery. They concluded that a single preoperative oral dose of gabapentin 600 mg given 1 h prior to surgery does not reduce postoperative pain scores, opioid consumption, or opioid-related side effects.[161]

Also, **Clarke and Pereira et al**,[162] had found that a single 600 mg dose of gabapentin given pre-operatively or post-operatively does not reduce morphine consumption or pain scores in hospital or at 6 months after hip arthroplasty within the context of spinal anesthesia and a robust multimodal analgesia regimen (patients received preoperative gabapentin versus placebo and all patients received postoperative acetaminophen, celecoxib and morphine PCA).[162]

Also, **Adam et al**[163] found that a single preoperative dose of 800mg of gabapentin did not augment post-operative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery.[163] Similarly, **Brogly et al**,[164] found that patients undergoing a thyroidectomy and receiving a single preemptive dose of 1200mg of

gabapentin within the context of cervical plexus blocks did not experience a reduction in acute pain or opioid consumption. However, a single 1200 mg dose of gabapentin did prevent delayed neuropathic pain at six months compared with the patients who received placebo.[164]

Due to the ability of local anesthetics to effectively block pain which decreases morphine consumption in the acute post-surgical period beside efficient multimodal analgesic regimen used in previously described studies may be the causes of insignificant role of gabapentin on postoperative pain after regional anaesthesia. It was obvious that studies looking at gabapentin in association with regional anesthesia techniques have yielded mixed results which need further investigations with respect to the timing and the duration of administration post-operatively.

As regard the time of first postoperative analgesic request, the present study showed that it was significantly prolonged in gabapentin group compared to the control group.

In agreement with the results of present study, **Pathalk et al**[165], in a previously described study found that time to the first postoperative analgesic demand was significantly longer in gabapentin group (145.34 min) than in control group (26.30 min). Similarly, **Najafi Anaraki et al**,[155] found the need for rescue analgesic drug was earlier in the fentanyl group than the gabapentin group.

Also, **Mohammed et al**[166] studied 80 patients scheduled to undergo elective FESS under general anesthesia. Patients were randomly assigned to receive oral placebo or gabapentin 1.2 g 1 h before surgery. They concluded that time until the first request for analgesia (morphine) in the PACU was longer and values of morphine consumption were lower in gabapentin group.

In contrast to the results of present study, **Mahoori et al**[167] studied the effect of pre-operative oral gabapentin 400mg on post-operative pain after herniorrhaphy with spinal anaesthesia. They found no significant difference between the first times of analgesic request among the two groups however it was longer in gabapentin group (40.8 ± 84 min versus 86.4 ± 82.2 min).[167]

As regard total postoperative analgesic requirements in the present study, there was significant lower total nalbuphine consumption in gabapentin group compared to control group.

In agreement with the results of present study, **Alayed et al**[168] included 14 trials on women scheduled for total abdominal hysterectomy, with or without bilateral salpingo-oophorectomy, under general anesthesia. Trials consisted of 448 cases in the gabapentin group and 443 others in the control group. There was a significant decrease in morphine consumption at 24 h when gabapentin was administered before surgery (from 24.3±55.9 mg to 13.2±42.7 mg) as well before and after surgery (from 25.7±80 mg to 20.3±55 mg) respectively. Analysis of results showed that effect of gabapentin in reducing morphine consumption (compared to placebo) at 24 h was stronger in the preoperative group than in the preoperative and postoperative groups.

Also, **Jadeja et al**[169], concluded that using 1200mg of oral gabapentin 2h before upper abdominal surgeries had decreased total tramadol consumption in gabapentin group compared to placebo.

Also, **Menigaux et al**[170] concluded 40 patients undergoing arthroscopic anterior cruciate ligament repair under general anesthesia. Patients were randomized into 2 groups (each of 20 patients) to receive 1.2 g oral gabapentin or placebo 1-2 h before surgery. They concluded that premedication with oral gabapentin reduced postoperative morphine consumption by 50% without producing side effects.

In contrast to the results of present study, **Deniz et al**[171] concluded that preoperative administration of oral gabapentin 900 mg did not decrease overall tramadol consumption when given to patients undergoing retropubic radical prostatectomy 2 h before surgery. However it decreased pain scores in the early postoperative phase (at 45 min, 60 min and 2 h) and reduced the need for rescue analgesia without serious side-effects. However the previously described **Srivastava et al**,[152] used a similar tramadol PCA regimen, and reported a significant decrease (33%) in tramadol consumption with gabapentin.

The difference between both studies was attributed to different methods used for inadequate pain relief as **Srivastava et al**[152] used a bolus dose of 50mg tramadol followed by 20 mg on demand, with a lockout interval of 20 min (maximum dose, 240 mg in 4 h). However, they allowed a 30 mg increase in tramadol at any time if analgesia was inadequate and they did not use rescue analgesia. **Deniz et al** [171] used (a lockout interval of 15 min) with rescue analgesia consisted of 1 g paracetamol IV, with 75 mg diclofenac sodium, administered IM if paracetamol proved to be inadequate. Moreover, radical retropubic prostatectomy is more painful than minilap open cholecystectomy and gabapentin may not show as great an opioid sparing effect after very painful surgeries compared with those that are less painful.[171]

As regard postoperative sedation assessment, the present study showed that sedation score was significantly increased in gabapentin group during the first postoperative 2 hours. Also, there were insignificantly increased sedation scores over most of the remaining times of assessment. This may be explained by sedative effect of gabapentin in addition to its favorable pain scores.

In agreement with the results of present study, **Ho et al**[172] included 16 valid randomized controlled trials to evaluate the efficacy and tolerability of perioperative gabapentin administration for the control of acute postoperative pain. The results showed that when gabapentin was administered at doses less than 1200 mg, pain intensity was also lower at 6 h and 24 h. Cumulative 24 h opioid consumption was also lower. But these favorite results were observed at the expense of increased risk of sedation however; it is desirable before and immediately after surgery.[172]

Also, this came in agreement with the previously described **Srivastava et al**[152] and **Tiippana et al**[154] studies who found gabapentinoids increase the incidence of sedation.

In contrast to the results of present study, Sedation scores were similar at all the measured times in the previously described study of **Turan et al.**[146]

As regard to PONV, the present study showed that gabapentin decreased it significantly which may be attributed to its antiemetic effect proved by different studies. Moreover, gabapentin significantly decreased the need for postoperative opioid analgesia consumption which is a known risk factor for increased incidence of PONV.

In agreement with the results of present study, a review of **Guttuso et al**[173] showed that out of 33 clinical trials reviewed, 12 studies provided a grade (A) recommendation for gabapentin use in treating PONV, a grade (B) recommendation for use in treating chemotherapy induced nausea and vomiting, and a grade (C) recommendation for use in treating hyperemesis gravidarum. Further research is needed to confirm these initial promising results, which implicate the alpha-2delta VGCC subunit as a novel therapeutic target in the treatment of several nausea and vomiting-associated clinical conditions.[173]

This came in agreement with **Ajori et al**,[174] where 140 included patients were randomly assigned to one of two groups (gabapentin or placebo), in a double-blind manner before hysterectomy. The study concluded that pre-emptive use of gabapentin 600 mg orally, significantly decreases PONV and anti emetic drug requirements.

This also came in agreement of previously described **Alayed et al**[168] and **Srivastava et al** [152] studies, who found gabapentin effective in decreasing PONV.

In contrast to the results of present study, **Marashi et al,**[175] compared the effect of clonidine and gabapentin on postoperative pain and PONV in 66 adult patients scheduled for thyroidectomy. Patients were randomly allocated to orally receive clonidine 0.2 mg, placebo or gabapentin 900 mg 2 h before thyroidectomy. They concluded that oral premedication with gabapentin or clonidine significantly decreases the post-operative pain and morphine consumption, without any decrease in PONV.

Also, **Sayal et al**[129] carried out a double-blind randomized and controlled study in 120 patients undergoing elective open cholecystectomy under general anesthesia. The patients were divided into 4 groups to orally receive placebo, acetaminophen 1 g, gabapentin 1.2 g or acetaminophen 1g plus gabapentin 1.2 g. They found that PONV in patients who consumed Gabapentin was 36.66% higher than the patients who were given acetaminophen / placebo ($P<0.001$). This may be explained by using tramadol as rescue analgesic which might have increased the incidence of PONV.[129]

Also, **Bhandari et al,**[176] studied the effect of gabapentin on PONV in patients undergoing elective laparoscopic cholecystectomy under general anesthesia. Forty patients were randomized to receive 600 mg gabapentin or a matching placebo. Gabapentin was given orally 2 h before surgery and 12 h after the first dose. Patients in both groups received diclofenac sodium 75 mg IM twice daily for pain and ondansetron 4 mg iv. They found no significant reduction in PONV score or antiemetic consumption between the two groups for a period of 24 h.

Disagreement might be due to the fact that **Bhandari et al** did not use opioids which are well-known to increase the incidence of PONV. Moreover, this study had fewer number of patients compared to other studies. Lastly, this study excluded patients who had motion sickness which are well-known to have increased incidence of PONV.[176]

Turan et al,[177] studied 50 patients who underwent rhinoplasty or endoscopic sinus surgery. Patients received either oral placebo or gabapentin 1200 mg 1 h before surgery. After standard premedication, 25 patients in each group received propofol, fentanyl, and local anesthesia at the operative site. Diclofenac 75 mg IM was administered as a rescue analgesic drug. They did not find significant difference in PONV score or antiemetic consumption between both groups.[177] **Turan et al** did not use opioids in the postoperative period which may contribute to decreased incidence of PONV in both groups.

Data collected from previous studies together with the present study can support that gabapentin has more recently extended into the management of more acute conditions, particularly in the perioperative period. More than 30 clinical trials evaluating the potential roles of gabapentin for postoperative analgesia and for reducing opioids consumption, preoperative anxiolysis, prevention of chronic post-surgical pain, attenuation of haemodynamic response to direct laryngoscopy and intubation, prevention of PONV, and postoperative delirium have been published. These favorable effects of gabapentin had added to the fact that gabapentin is a perioperative multimodal drug proved by many studies.[125, 178]

The wide variability of gabapentin dosing regimens, which varied between 300 and 1800 mg and the differences in pain score and side-effect evaluating systems and type of surgeries undoubtedly, influences the outcome of these studies. Therefore to determine definite effect of gabapentin, we should consider favorite dosage for each type of surgery especially for major surgeries.

SUMMARY

Nowadays, obesity represents a worldwide public health issue due to its epidemic proportions, associated co morbidities and tremendous medical and social costs. Recently, bariatric surgery is the most efficient method to reduce weight and to maintain it in patients with BMI >35 kg/m^2 with associated severe co morbidities, as well as in those with BMI >40 kg/m^2. Weight loss of 5–10% of initial body weight can improve glucose intolerance, type 2 diabetes mellitus, hypertension, hyperlipidaemias and many other comorbidities.

Since the introduction of laparoscopic as alternative to traditional open surgery, postoperative pain has been generally reduced. However, it can still peak, especially during the early postoperative period and becomes the main cause of overnight hospital stay and prolonged convalescence. If sufficient analgesia is provided, not only will the patient's comfort be increased but duration of hospital stay will be shortened, reducing both treatment costs and risk of hospital-acquired infections. Optimal analgesia also ensures adequate ventilation and pulmonary mechanics and reduces risk of postoperative chest infections.

Post-operative pain is not purely nociceptive in nature and consists of inflammatory, neurogenic, and visceral components. Though opiates were used for long, to ameliorate such pain, yet still this was at the expense of concurrently inducing respiratory depression, sedation, PONV, pruritus, urinary retention, ileus, and constipation that can delay hospital discharge and contribute to unanticipated admission especially in obese patients. Thus, optimizing postoperative pain relief, not only to sub-serve reduction of its intensity but to also enhance the recovery and shorten length of stay became the broader target of multimodal pain control regimens. That is why; searching for a drug that would be effective in reducing pain, safe from major adverse effects and can meanwhile possess an opioid-sparing potentiality would be a merit so as to improve the success rate of bariatric surgery. Therefore, multimodal analgesia utilizing drugs acting on different analgesic mechanisms is becoming increasingly popular.

Preemptive analgesia is the treatment that prevents establishment of central sensitization caused by incisional and inflammatory injuries. It starts before incision and covers both the period of surgery and the initial postoperative period. It could be achieved by using different analgesic drugs that work at different sites or by using a combination of drugs which would provide a positive synergistic action. Gabapentin and paracetamol are two commonly used agents for this purpose.

Analgesic effect of Paracetamol is thought to be through inhibition of prostaglandins synthesis in the central nervous system, peripheral blocking of pain impulse generation, serotonergic and a cannabinoid agonism mechanisms. Gabapentin is a structural analogue of gamma-amino butyric acid which binds to the α-2-δ subunit of voltage-dependent calcium channels that are widely distributed in spinal cord and brain. By altering calcium currents, gabapentin reduces or modulates the release of several excitatory neurotransmitters producing inhibitory modulation of over-excited neurons and returning them to a normal state.

Thus the present study was carried out to evaluate the effects of single pre-emptive dose of paracetamol with or without gabapentin on post-operative pain after laparoscopic sleeve gastrectomy under general anesthesia.

The present study was carried out at Alexandria University main hospital; on 50 patients, ASA I and II, of both sexes, aged 18-50 years, having BMI > 35 and scheduled for laparoscopic sleeve gastrectomy. Patients were randomly categorized into two groups (each of 25 patients) according to closed envelope method.

After a detailed history taking, proper clinical examination and routine laboratory investigations, all patients were premedicated with IV ranitidine 50 mg and IV metoclopramide 10 mg on the night before surgery and another dose was given one hour prior to induction of anaesthesia via a 20gauge intravenous line. Then, patients received:

Group (I): **(control group)**: patients received 1 g paracetamol by intravenous infusion (IVI) 30 minutes before induction of anaesthesia.

Group (II): **(gabapentin group):** patients received 1.2 g oral gabapentin 2 h preoperatively plus 1 g paracetamol IVI 30 minutes before induction of anaesthesia

At operation room, all patients were connected to the standard monitoring; including electrocardiograph, non-invasive arterial blood pressure and pulse oximeter.

After Preoxygenation for 5 minutes, IV induction for all patients was achieved by fentanyl 1µg/kg lean body weight (LBW), propofol 2 mg/kg (LBW) and rocuronium 1 mg/kg ideal body weight (IBW). Endotracheal intubation was confirmed by $EtCO_2$ and chest auscultation. A nasogastric tube was inserted to decompress the stomach. Anaesthesia was maintained with isoflurane 1.5% in 100% oxygen and rocuronium (0.1 mg/kg IBW) guided by nerve stimulator till the end of surgery. Tidal volume was set to 8 ml/kg and respiratory rate was adjusted to maintain EtCO2 level at 35-40mmHg. Fentanyl increments were given every 30min intraoperatively (0.5µg/kg LBW) but not within 30min of the estimated end of the operation. All patients received IV ketorolac (0.5mg/kg IBW) and IV ondansetron 4mg at the end of surgery. Neuromuscular paralysis was reversed with neostigmine (0.05 mg/kg LBW) and atropine (0.02 mg/kg IBW). After a satisfactory recovery, patients were extubated and discharged to ICU. Patients received regular IV ketorolac (0.5mg/kg IBW)/6h started 6h after the intraoperative dose. Nalbuphine was used as rescue analgesia when VAS was ≥ 4 at rest or ≥ 7 on movement. Ondansetron 4mg IV was used to treat PONV grade II-III.

The following parameters were assessed in the present study:

1- Demographic data: as regard age, sex, duration of surgery and body mass index.

2- Hemodynamic parameters: heart rate, mean arterial blood pressure and arterial oxygen saturation were measured 2h before induction (base line data), just before induction of anaesthesia, just before endotracheal intubation, immediately after endotracheal intubation, every 30 min intraoperatively for 3h, immediately after endotracheal extubation and every 6 h postoperatively for 24h.

3- Postoperative pain: was scored both at rest (static) and during cough (dynamic), using the VAS. Assessment of pain began on arrival of patient to on arrival of patient to ICU (zero time), every 30 minutes in the first 2h then; every hour till 6h then every 2h for the rest of 24 h.

4- Total analgesic requirements: When postoperative pain is VAS ≥ 4 at rest or ≥ 7 on movement, patients will receive 6mg nalbuphine IV and VAS is assessed 30 minutes after nalbuphine then the total administered dose and requirement time will be recorded over 24h.

5- Time of first rescue analgesia will be recorded and compared in both study groups.

6- Level of sedation: was assessed with the Ramsay Sedation Scale Assessment of sedation will be done on arrival of patient to ICU (0) and then every 2 hrs till the end of the study, that is, 24 hrs after operation.

7- Postoperative nausea and vomiting: were observed during the first 24 postoperative and properly treated by ondansetron 4mg when PONV grade ≥ 2.

8- Any other side effects of gabapentin during the first 24 hours postoperative were recorded and properly treated like dizziness, vertigo, ataxia, nystagmus, urinary retention, dry mouth, etc…

Results of the present work cleared that there was no statistically significant difference between the two groups as regards age, sex or body mass index.

Regarding the hemodynamic parameters, the reduction in heart rate observed by gabapentin was found significant at all times of measurement except before endotracheal intubation and 12 h postoperatively where this decrease was insignificant, while the reduction in the mean arterial blood pressure observed by the drug was significant after endotracheal intubation, at 120 minutes intraoperatively, after extubation and during the whole postoperative period. Also, there was insignificant decrease just before induction of anaesthesia, just before intubation, at 30, 60 and 120 min intraoperatively. There was no significant difference in SPO_2% between the gabapentin and control groups.

Focusing on post-operative pain, the use of gabapentin 1.2 g pre-operatively, succeeded to significantly attenuate the pain intensity, as judged by the reduction in VAS (whether static or dynamic). On static pain assessment, there was a significant lower VAS in gabapentin group over all times of measurement except at 3, 5, 7, 8, 10 and 22h where this decrease was insignificant. On dynamic pain assessment, there was a significant lower VAS at all times of assessment except at 3 and 18h postoperatively where this decrease was insignificant. The time needed for initiation of first dose of nalbuphine was significantly delayed to a mean of 137.80±95.28 min. compared to 55.12±64.50 min. in the control group. Moreover, the total dose of nalbuphine consumed during the studied time postoperatively, was also significantly reduced by gabapentin (10.56±4.34) in comparison to control (17.76±6.36 mg/24h).

Using Ramsey sedation score, gabapentin caused higher level of sedation at zero time and 2 h postoperatively. It was insignificantly higher in gabapentin group during the remaining times of measurement except at 6 and 18 h when it was insignificantly higher in the control group.

Regarding post-operative nausea and vomiting, there was a significant decrease of PONV with gabapentin compared to control group during postoperative 24h. No statistical difference was observed between gabapentin and control groups regarding the presence or absence of other side effects along the 24h postoperative study period.

In conclusion, this study validates the efficacy of pre-operative administration of oral gabapentin in a dose of 1.2 g given 2 h before surgery, in significantly attenuating pain intensity and total nalbuphine consumption during the first 24 hours postoperatively. It also confirmed that the drug could manage to significantly delay the time needed for initiation of nalbuphine analgesics throughout the post-operative period. The study further verified that the drug possessed a safe haemodynamic profile, can ameliorate the stress response to laryngoscopy and tracheal intubation and stress related to pneumoperitoneum. Also, this study has verified that gabapentin was free from inducing respiratory depression as there was no alteration in O2 saturation or O2 requirements. The study meanwhile ruled out any involvement of side effects induced by the tested dose of the drug, during the first 24 hours postoperatively.

CONCLUSIONS

1- A single 1.2 g of pre-emptive gabapentin could significantly ameliorate the intensity of post-operative pain after laparoscopic sleeve gastrectomy.

2- Preoperative gabapentin could significantly reduce opiate consumption and delay the time needed for initiation of any analgesics in the first 24 hours postoperatively.

3- Single preoperative 1.2 g of gabapentin could significantly reduce stress of laryngoscopy and intubation. It could offer much more haemodynamic stability during pneumoperitoneum and postoperative period.

4- The same dose of preoperative gabapentin increases sedation score postoperatively.

5- The use of such pre-operative dose of gabapentin could decrease the incidence of PONV but increases the incidence of postoperative sedation.