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Review Article

The Role of Intravenous Ketamine for Enhanced Recovery after Surgery (ERAS) Protocol for Acute Postoperative Pain Management after Laparoscopic Hysterectomy -

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ABSTRACT

At the 'ripe age of fifty years', Ketamine is still considered a 'newcomer' in pain medicine, recommended as one of the modes of multimodal analgesia techniques available after common surgical procedures for pain relief and to reduce the requirement of Morphine in an acute setting after trauma, hence helping early recovery and discharge, perhaps beneficial for enhanced recovery.

The intention of the review was to evaluate the usefulness of Intravenous (IV) Ketamine in the perioperative period to manage acute postoperative pain, to recommend its inclusion for the ERAS acute pain protocol after laparoscopic hysterectomies. PubMed, Medline, Scopus, Embase, Cochrane, Web of knowledge and Google Scholar were searched with keywords 'Ketamine', 'Intravenous', 'IV', 'acute pain', 'postoperative pain', 'major abdominal surgeries', 'abdominal hysterectomies', limiting to past 10 years and English language.

Three major regimens for the use of Ketamine for this purpose were examined individually, the pre-emptive, a bolus with an infusion and as an adjunct to an opioid PCA. Although an attempt was made to segregate the regimens to explore them specifically, there was an overlap of these regimens in some of the studies, making it difficult to draw any definitive conclusions.

However, of the three major regimens examined, the pre-emptive method appears to have got the maximum number of high level evidence to support this use of IV Ketamine for postoperative pain relief after laparoscopic hysterectomies.

INTRODUCTION

Acute pain is pain of short duration of 3-6 months, which is generally described as sharp or throbbing which serves as warning to the body, of disease or threat, which may be due to surgery, dental work or trauma like broken bones, burns or cuts or labour and childbirth [1].

Despite the ongoing developments in the management of acute pain in the past twenty years, 40% of the population still report a great amount of pain, after surgical procedures, as reported by the Australian and New Zealand College of Anaesthetists (Table 1) [2].

Acute postoperative pain has been proven to lead to chronic pain if not treated adequately, besides having other adverse effects such as cardiovascular, respiratory, neurological, psychosocial, endocrinological compromise with hyperglycaemia, insulin resistance and an increased rate of infection and the associated reduced patient comfort and satisfaction [3]. Opioids have been the traditional recommended mode used in the management of acute pain, aiming at central mechanism of pain perception [4]. However, Mariano proposed the use of many drugs and methods, acting synergistically at different sites of pain pathway, in a multimodal approach, to reduce this pain. This may be with drugs like opioids, Paracetamol, Nonsteroidal Anti-Inflammatory Drugs (NSAIDS), cox2 inhibitors and with regional techniques (neuraxial and nerve blocks) or non-pharmacological (Trans-Electric Nerve Stimulator (TENS), acupuncture, music, meditation, hypnotherapy) [3], to minimise the side effects of one single drug at high doses.

Both the ASA-TFAPM [5] and ANZCA [2] provide similar recommendations to manage acute pain with an emphasis on multimodal techniques, including educating the patients and their families preoperatively. Synergistic action of the many modes and drugs available reduces side effects of individual drugs, permitting earlier recovery and discharge, the basic concept of Enhanced Recovery after Surgery (ERAS) [6].

Ketamine is one of the drugs recommended by Gritsenko, et al. [7] in their review of various modes of multimodal analgesia techniques available after common surgical procedures, based on review of research evidence provided by the Procedure Specific Postoperative Pain Management (PROSPECT) group. Ketamine for pain relief has been shown to reduce the requirement of Morphine in an acute setting after trauma [8,9]. Sjövall, et al. [10] reviewed the literature to provide evidence for postoperative pain management after laparoscopic procedures and suggest a multimodal approach due to the multiple origin of this type of pain. Ketamine is one of the modes suggested by them.

- Intravenous (IV) Ketamine may be administered at different time intervals peri-operatively in various regimens [11] to provide acute postoperative pain relief:IV just after induction and 10-15 minutes before the skin incision when it is said to be pre-emptive
- As bolus just at induction and continued as an IV infusion intra and postoperatively
- Added to the PCA morphine postoperatively for 24 to 48 hours [11-13].

The dose of Ketamine for these regimens has still not been definitively established [14], but have been evaluated in various regimens, using sub-anaesthetic dose of 0.1-1.5mg/kg [13,14], with 2mg/kg IV Ketamine being the anaesthetic dose [15].

The aims of this review are to critically evaluate:

- The evidence on the role of pre-emptive IV Ketamine for acute pain management,
- The effectiveness and side effect profile of adding Ketamine to the Morphine PCA
- The evidence on the use of intravenous Ketamine at induction followed by an IV infusion and its effect on postoperative pain, side effects and opioid consumption after abdominal surgeries and extrapolate this to laparoscopic hysterectomies,
- Try to establish and reflect on whether there is sufficient evidence to support its inclusion into the ERAS protocol for laparoscopic hysterectomies

METHOD OF LITERATURE SEARCH

PUBMED, MEDLINE, SCOPUS, COCHRANE, Google Scholar and Web of Knowledge were searched. An attempt was made to select studies with a focus on evaluating the use of Ketamine for postoperative analgesia, both to reduce pain and opioid consumption after laparoscopic hysterectomy, but due to paucity of studies specifically on this type of surgery, studies on all types of abdominal surgery were selected, de-duplicating same studies from different databases. Eventually, 3 SR, 1 quantitative research, one retrospective study and 13 RCTs were shortlisted, for this literature review. One

Table 1: Summary of recommendations (ASA-TFAPM 2012, pp 255-257).

I. Institutional Policies and Procedures for Providing Perioperative Pain Management

- Ongoing education and training to ensure that hospital personnel are knowledgeable and skilled
- Epidural analgesia, PCA, and various regional anaesthesia techniques and nonpharmacologic techniques (*e.g.*, relaxation, imagery, hypnotic methods)
- Anaesthesiologists providing perioperative analgesia services should do so within the framework of an Acute Pain Service.

II. Preoperative Evaluation of the Patient

- Directed pain history, directed physical examination, and pain control plan should be included in the anaesthetic preoperative evaluation.

III. Preoperative Preparation of the Patient

- Appropriate adjustments or continuation of medications to avert an abstinence syndrome, treatment of preexistent pain, or preoperative initiation of therapy for postoperative pain management.
- Patient and family education regarding their important roles in achieving comfort, reporting pain, and in proper use of the recommended analgesic methods, including behavioural modalities for control of pain and anxiety.

IV. Perioperative Techniques for Pain Management

- Therapeutic options such as epidural or intrathecal opioids, systemic opioid PCA, and regional techniques, in preference to intramuscular opioids ordered "as needed."
- Special caution should be taken when continuous infusion modalities are used because drug accumulation may contribute to adverse events.

V. Multimodal Techniques for Pain Management

- Whenever possible, anaesthesiologists should use multimodal pain management therapy.
- Unless contraindicated, patients should receive an around the clock regimen of NSAIDs, COXIBs, or acetaminophen.
- Regional blockade with local anaesthetics should be considered.

Perioperative Techniques for Pain Management

Epidural or intrathecal analgesia with opioids (*vs.* epidural placebo, epidural local anaesthetics, or IV, intramuscular, or oral opioids)
Patient-controlled analgesia with opioids:
IV PCA *versus* nurse-controlled or continuous IV
IV PCA *versus* intramuscular
Epidural PCA *versus* epidural bolus or infusion
Epidural PCA *versus* IV PCA
IV PCA with background infusion of opioids *versus* no background infusion
Regional analgesia with local anaesthetics or opioids
Intercostal or interpleural blocks
Plexus and other blocks
Intraarticular opioids, local anaesthetics or combinations
Infiltration of incisions

Multimodal Techniques (Epidural, IV, or Regional Techniques)

Two or more analgesic agents, one route *versus* a single agent, one route
Epidural or intrathecal analgesia with opioids combined with:
Local anaesthetics *versus* epidural opioids
Local anaesthetics *versus* epidural local anaesthetics
Clonidine *versus* epidural opioids
IV opioids combined with:
Clonidine *versus* IV opioids
Ketorolac *versus* IV opioids
Ketamine *versus* IV opioids
Oral opioids combined with NSAIDs, COXIBs, or acetaminophen *versus* oral opioids

VI. Patient Subpopulations

• Geriatric patients

- Pain assessment and therapy should be integrated into the perioperative care of geriatric patients.
- Anaesthesiologists should recognize that geriatric patients may respond differently than younger patients to pain and analgesic medications, often because of comorbidity.
- Vigilant dose titration is necessary to ensure adequate treatment while avoiding adverse effects such as somnolence in this vulnerable group, who are often taking other medications (including alternative and complementary agents).

• Other subpopulations

- Anaesthesiologists should recognize that patients who are critically ill, cognitively impaired, or have communication difficulties may require additional interventions to ensure optimal perioperative pain management.
- Anaesthesiologists should consider a therapeutic trial of an analgesic in patients with increased blood pressure and heart rate or agitated behaviour when causes other than pain have been excluded

RCT had to be discounted as it was a study on intramuscular route of Ketamine administration. However, one study using subcutaneous Ketamine was included as it compared this with the IV route. One dated study from 2004 was included as it was specifically on the use of Ketamine for laparoscopic gynaecological procedures, which conforms more to the specific focus of this review (Figure 1).

The Critical Appraisal Skills Programme (CASP) [16] critical appraisal tools were used for critical analysis of the Randomised Controlled Trials (RCTs) and Systematic Review (SR) and the Harbour and Miller (2001) Hierarchy [17] scale to rate the levels of evidence.

LITERATURE REVIEW

One dated study by Kwok, et al. [18] (Figure 2) compared the analgesic requirements of pre-emptive and postsurgical IV Ketamine on postoperative pain relief specifically after laparoscopic gynaecological procedures found on it to be more effective pre-emptively. A systematic review by Laskowski, et al. [13] examined all these regimens of Ketamine. They found that peri-operatively,

Keywords for all databases	'Ketamine', 'acute pain management', 'Postoperative pain management', 'laparoscopic hysterectomy', 'pain relief', 'pain', pain scores', 'opioid consumption', 'side effects'
Databases searched	
OVID Medline, PubMed , Embase	521 studies Limiting to 'intravenous', 'IV', English language, humans and past five years, removing duplicates: 128 studies Ketamine in Abdominal surgeries:22 Clinical studies and RCTs: 17; 2 on Caesarean section and one letter discounted Meta-analysis and SR: 4 and 1
Scopus	100 relevant studies on Ketamine for acute pain 28 of them shortlisted with general discussion on postoperative pain management and ERAS protocols 3 SR and 12 RCTs on use of Ketamine for postoperative pain in abdominal procedures
Cochrane	111 reviews and trials 75 on abdominal and gynaecological surgeries 1 SR and 10 RCTs since 2010
Web of Science/Knowledge	19 studies 9 on Ketamine and abdominal surgery

Figure 1: Literature Search undertaken .
SR: Systematic Review; RCT: Randomised Controlled Trial

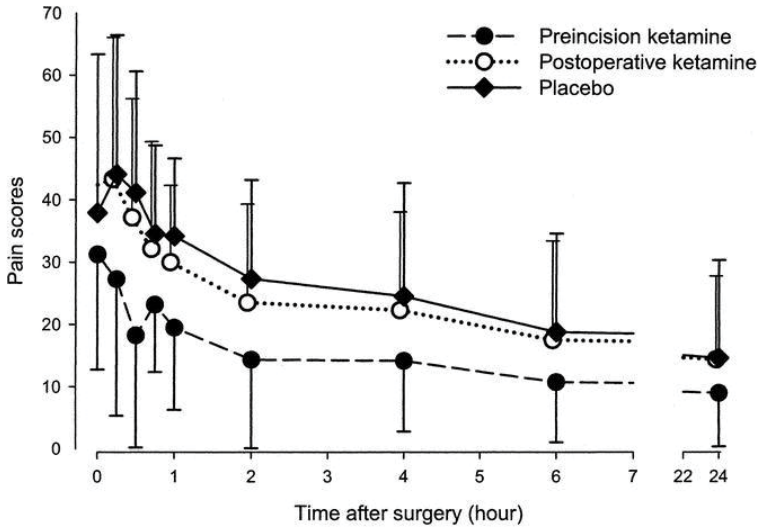

Figure 2: (Kwok, et al. 2004, p 1046) Pain scores after surgery, measured on a 100-mm Visual Analogue Scale (VAS). Data points are displayed slightly offset for clarity. Values are mean _sd (permission obtained)

Ketamine did reduce the consumption of opioids postoperatively with reduced pain scores, more so with upper and lower abdominal procedures, with no serious side effects. Any hallucinations associated with it could be countered effectively with the concomitant use of benzodiazepines which was done in most studies. The timing of Ketamine administration, whether pre or post incision or pre-emptive, or its dose made no difference to its analgesic efficacy (pre-incision SDM - 0.562; post-incision SDM -0.751), with the SDMs between the two not being too different from one another (Table 2).

Pre-emptive ketamine

Four studies on the pre-emptive regimen of Ketamine were all RCTs using IV Ketamine in the doses ranging from 0.1 to 1mg/kg, all showing reduced pain scores and opioid sparing effects. Safavi, et

Table 2: Results for Laskowski et al.'s (2011, p 919) SR (permission obtained).

Subgroup	Member	Study treatment arms	Effect Size (SDM)	Lower 95% CI	Upper 95% CI
Age	Adult	58	-0.685	-0.862	-0.508
	Pediatric	4	+0.173	-0.147	+0.492
Ketamine Dose	≤ 0.5 mg/kg	32	-0.589	-0.813	-0.366
	0.501-1 mg/kg	6	-0.038	-0.252	+0.175
	> 1 mg/kg	20	-0.808	-1.121	-0.496
Mode of Delivery	Bolus +/- PCA	29	-0.497	-0.729	-0.265
	Infusion +/- PCA	29	-0.782	-1.055	-0.509
	PCA alone	4	-0.496	-1.106	+0.114
	Bolus alone	27	-0.55	-0.79	-0.31
Timing	Pre-incision	39	-0.562	-0.773	-0.35
	Post-incision	23	-0.751	-1.05	-0.452
Intraop opioid	Fentanyl	24	-0.611	-0.857	-0.364
	Sufentanyl	5	-0.738	-1.051	-0.426
	Remifentanil	17	-0.709	-1.145	-0.274
	Other	16	-0.511	-0.85	-0.172
Surgical site	Head and Neck	5	+0.065	-0.201	+0.331
	Orthopedic	17	-0.811	-1.158	-0.464
	Lower and mid abdomen	26	-0.471	-0.719	-0.222
	Upper abdomin and thoracic	6	-1.741	-2.625	-0.857
	Other	8	-0.536	-0.778	-0.293
Pain Severity	< 4/10	6	-0.437	-1.209	+0.335
	4 to 4.9/10	17	-0.475	-0.767	-0.183
	5/10 to 6.9/10	24	-0.518	-0.749	-0.287
	> 7/10	13	-1.063	-1.521	-0.605
N_2o use	Yes	39	-0.731	-0.944	-0.518
	No	17	-0.433	-0.84	-0.026
	Not specified or optional	6	-0.555	-0.841	-0.269

al. [3] found both Subcutaneous (SC) and IV routes to be effective pre-emptively in patients undergoing open cholecystectomy, in a randomised double blinded placebo-controlled trial. Behdad, et al. [19] obtained promising results with pre-emptive IV Ketamine by improving the postoperative analgesia after appendectomy. A double blinded, placebo-controlled RCT by Gharaei, et al. [20] established the opioid sparing effect of Ketamine when given pre-emptively to opioid abusers who underwent Extracorporeal Shock Wave Lithotripsy (ESWL). Wang, et al. [21] concluded that administering IV Ketamine pre-emptively reduced the postoperative pain with minimal side effects from an RCT on patients undergoing Transurethral Resection of Prostrate (TURP). The above studies achieved a level of evidence varying between 2- to 2+ [17].

Ketamine with PCA Morphine

The RCTs and meta-analyses reviewed for this regimen showed varied results. A literature review by Jouguelet-Lacoste, et al. [14] found only few studies where Ketamine was effectively used postoperatively, added to the Morphine or Hydromorphone PCA. These studies [22,23] used a dose of 0.15-0.2 mg/kg/hr [sub-anaesthetic(15)] for their regimens, showing synergistic effect with other drugs, reducing doses of each of them and respective side effects. Lo, et al. [24] found no difference in the pain scores with this intervention in women who were scheduled for abdominal hysterectomy. A qualitative review by Carstensen, et al. [25] did show that the majority of the studies were found on abdominal surgeries, of which 50% were on abdominal hysterectomy cases where Ketamine was added to the Morphine PCA. These studies also ranked higher on the five point Oxford Quality scale. However, in terms of the number of patients included from the various studies, a greater number of them (512 as against 333) showed no difference in pain scores or side effect with the inclusion of Ketamine to the Morphine PCA. But, Ketamine was found to be safe and effective to be administered as an adjuvant to Morphine or Hyrdromorphone PCA in the systematic review by Wang, et al. [26] and also by the meta-analysis by Ding, et al. [27]. Both of these [26,27] being a higher level of evidence, besides being the more recent ones, their findings would refute the ones from the earlier qualitative analysis by Carnesten, et al. [25] and the RCT by Lo, et al. [24], which did not find Ketamine to be useful for this purpose.

Ketamine as perioperative IV bolus and infusion

The literature reviews and RCTs for this regimen found Ketamine, as bolus and infusion, in various regimens showed positive, promising

results, the dosage being quite varied and expressed in different units, to be effective for postoperative pain relief. The bolus doses were all between 0.15 mg to 0.5 mg/kg, with minimal side effects, while the infusions were expressed as 0.2 mg/kg/hr (200 mcg/kg/hr), while some infusions have been administered as 2mcg/kg/min, which would amount to 120 mcg/kg/hr. But surprisingly, studies which used higher doses of 200 mcg/kg/hr [23,28], did not find Ketamine to be useful, probably because these study methodologies lacked good rigour, while the ones using the lower doses of 120 mcg/kg/hr [29-31] have all shown encouraging results.

As Ketamine is an anaesthetic agent by itself, it could be used for the induction as IV bolus (2 mg/kg) [15] and continued as an infusion thereafter for different periods of time to ensure adequate postoperative analgesia. No piece of literature has been found with this regimen. However, if being used as an analgesic agent only, it would need to be used at a sub-anaesthetic bolus dose (<2 mg/kg) [15] as an adjuvant to other anaesthetic induction agents, which may or may not be followed by the infusion thereafter.

The literature review by Jouguelet-Lacoste, et al. [14], from over 40yrs starting 1966 till 2013, found 5 meta-analyses, all of which found Ketamine to reduce postoperative pain scores and also opioid consumption by various routes of administration. They found bolus dose of Ketamine <1 mg/kg used commonly, followed by an infusion, which would vary from 0.1 mg-1mg /kg/hr, an infusion of 1.2 mg/kg/hr showed the maximum of 40% reduction in pain scores and Morphine consumption [14].

Ketamine could be provided for postoperative pain relief in the various regimens [14]:

1. IV infusion only
2. Intraoperative bolus and intraoperative infusion of low-dose Ketamine
3. Intraoperative bolus and 2hr postoperative infusion of low-dose Ketamine
4. Intraoperative bolus and 24hr postoperative infusion of low-dose Ketamine
5. Intraoperative bolus and 48hr postoperative infusion of low-dose Ketamine

Different studies had different primary endpoints to assess their results, either reduction of Morphine consumption or pain VAS scores. Ketamine was found to be more effective in reducing the Morphine consumption than the VAS scores. Jouguelet-Lacoste, et al. [14] also reviewed literature on the use of IV Ketamine for various types of surgery. With respect to abdominal procedures in particular, they found eight trials, seven of which found definitive reduction in both opioid consumption and postoperative VAS scores with the IV Ketamine in various regimens [19]. An RCT by Zakine, et al. [29] found beneficial results to postoperative pain relief after major abdominal surgeries with perioperative IV Ketamine. Lak, et al. [30] found promising results in a double blinded RCT on 50 kidney donors to assess the pain relieving and opioid sparing effects of Ketamine administered postoperatively as an IV bolus and continued as infusion. Parikh, et al. [31], in their RCT on 60 patients scheduled for renal surgery, did find preoperative IV Ketamine bolus followed by an intraoperative infusion on postoperative pain and opioid consumption to be beneficial, but this study lacked a clear focus and a defined aim, resulting in heterogeneity of their results.

Major abdominal surgeries are prone to more pain, leading to immobility and thus increasing the risk of venous thrombosis and pulmonary complications. The 6-Minute Walk Distance (6-MWD), shown to correlate well with daily activities, is used to assess recovery after cardiac, thoracic and major abdominal surgeries [32], which in turn would indirectly assess the pain scores as activities would be possible only if pain were adequately controlled. Grady, et al. [28] did not find any difference in the 6-MWD or any of the secondary outcomes between the Ketamine or Lignocaine and their respective placebo groups ($p = 0.54$ and $p = 0.96$).

Stessel, et al. [33] compared the effects if s+ Ketamine with or without Magnesium on postoperative analgesia and PCA Piritramide requirements, when given as an IV bolus followed by an infusion intraoperatively tendency towards a reduced use of Opioid in Ketamine group. Piritramide is a synthetic opioid, used in Continental Europe over the past 50yrs, for postoperative pain relief [34]. However, there has been no experience in its use in the NHS, the editorial by Kumar and Rowbotham [34] not explaining this as well. Barreveld, et al. [23] found only small improvement in postoperative pain and reduction in Morphine requirements in patients on long long-term opioids for chronic pain, when Ketamine was given as an infusion along with the PCA. Jacobsohn, et al. [35] compared two analgesic regimens, one with and the other without Ketamine, on patients who underwent robotic radical cystectomy to determine that Ketamine could expedite the return of bowel function, besides improving pain relief, thus reducing the time of discharge. Khajavi, et al. [36] in a double blinded RCT, compared the analgesic efficacy of Ketamine and Tramadol when given postoperatively along with IV Paracetamol after open renal surgery and showed that adding Ketamine to Paracetamol for postoperative analgesia improved pain score and also reduced Morphine consumption; agitation and sedation score was better at 10 and 20 min. with the PT(Paracetamol/Tramadol) group, but were better for the PK (paracetamol/Ketamine) group when they left the recovery, though not statistically significant.

RESULTS

Out of the eighteen studies reviewed, fifteen of them found IV Ketamine useful for postoperative pain relief and reduction of opioid use, when used perioperatively in various regimens, all of these studies with promising results, scoring 2- to 1++ on the levels of evidence (17), the pre-emptive regimen showing an edge over others.

DISCUSSION

Acute post-surgical pain has been found to be due to nerve injury, inflammatory response and peripheral and central sensitisation, the latter at the spinal cord level, involving N-Methyl D-Aspartate (NMDA) receptors [2]. Ketamine, an NMDA receptor antagonist, has been found to reduce central sensitisation of nociceptors in sub-anaesthetic doses (<2 mg/kg) and also the postoperative pain by inhibiting c-fibre activity [3].

Professor Henrik Kehlet is credited with the idea of ERAS in the late 1990s, to provide a 'risk free pain free surgery' [6]. ERAS Society initiated in 2010, to implement multimodal perioperative care to achieve early recovery and discharge after major surgeries. The recommendations were originally for colorectal surgeries, with an epidural block being the main mode of analgesia. ERAS then got gradually implemented to other types of surgery like Urology and Gynaecology. One of their aims is to reduce use of opioids for

Table 3: Summary of RCTs on peri-operative IV Ketamine for acute postoperative pain management.

Authors (year)	Type of surgery	Ketamine protocol	Summary of results: Ketamine favoured or not for pain scores and opioid consumption	Level of evidence (Harbour and Miller 2001)
Kwok, et al. [18]	Laparoscopic gynaecological procedures	Pre-incision group: 0.15 mg/kg of Ketamine 15 min before incision Post-incision group: 0.15mg/kg of Ketamine after skin closure	Yes	2+
Laskowski et al. [13]	Systematic and meta-analysis	Major surgeries	Yes	1++
Safavi, et al. [3]	Open cholecystectomy	Pre-emptive: SC1 group: SC Ketamine: 1 mg/kg 10 min. before incision SC2 group: SC Ketamine: 2 mg/kg 10 min. before incision KI group: IV Ketamine 1 mg/kg, 10 min before incision	Yes, both by IV and SC routes; IV better	2+
Behdad, et al. [19]	Open appendectomy	Pre-emptive: 0.5 mg/kg of Ketamine 10 min before skin incision	Yes	2-
Gharaei, et al. [20]	ESWL	Pre-emptive: 0.1 mg/kg	Yes	2-
Wang, et al. [21]	TURP	Pre-emptive: 0.5 mg/kg of Ketamine 10 min before skin incision	Yes	2-
Lo et al. [24]	Abdominal hysterectomies	PCA with morphine, ratio of 1:1, 2 mg/ml of bolus	No	2- (assessment on day after surgery)
Zakine, et al. [29]	Major abdominal surgeries	Bolus and infusion: Peri group: 0.5 mg/kg of Ketamine 10 min before incision and 2 mcg/kg/min for 48hrs Intra group: 0.5 mg/kg of Ketamine 10 min before incision and 2 mcg/kg/min intraoperatively only	more positive results with peri group	2+
Lak, et. al. [30]	Kidney donors	Bolus postoperatively and infusion: 0.5 mg/kg Ketamine bolus before incision, 2 mcg/kg/min first 24hrs 1 mcg/kg/min next 24 hrs	yes	2-
Parikh, et al. [31]	Renal surgeries	Bolus and infusion: 0.15 mg/kg bolus, 2 mcg/kg/min infusion	Yes	2+
Grady et al. [28]	Abdominal hysterectomies	Bolus and infusion: 0.35 mg/kg bolus, 0.2 mg/kg/hr for 2hrs 0.12mg/kg/hr for 24hrs	No	2-
Stessel et al. [33]		Bolus and infusion: 0.2 mg/kg bolus 2 mcg/kg/min Ketamine	Yes	2-
Barreveld et al. [23]	Major surgeries	Infusion and opioid PCA: Ketamine 0.2 mg/kg/hr infusion with opioid PCA	No	
Jacobsohn et al. [35]	Robotic cystectomy in opioid dependents	Bolus and infusion: Intraoperative Ketamine bolus 0.5 mg/kg Postop infusion 5 ml/hr Oral Ketamine 20 mg 6 hrly	Yes	3
Khajavi et al. [36]	Open renal surgeries	Postop single bolus Ketamine 0.5 mg/kg along with Paracetamol Comparison with Tramadol 0.7 mg/kg	Ketamine better	2-
Carnesten et al. / qualitative review	Qualitative	Major surgeries	Yes, abdominal hysterectomies	3 (expert opinion)
Ding et al. [27]/SR with meta-analysis	Systematic and meta-analysis	Major surgeries	Yes	1-
Wang et al. [26]/ SR with meta-analysis	Systematic and meta-analysis	Major surgeries	yes	1-

postoperative pain to decrease the side effects of nausea and vomiting, which could expedite discharge from hospital after major operations [6].

An increasing number of surgical procedures are being performed laparoscopically the past two decades, perhaps with the intension of causing less pain due to smaller skin incisions. However, early pain after laparoscopic procedures can be equally painful as open procedures, if not more [37]. However, the many techniques introduced so far for acute postoperative pain management, have shown little benefit in achieving the goals of the ERAS [6]. Neuraxial blocks epidurals have been found to have side effects (NAP3), like hypotension. Hence other analgesic recipes for the ERAS are being explored (NAPS 2016), which include nerve blocks, Transabdominal Plane (TAP) block and analgesic adjuvants like Ketamine, Lidocaine and Magnesium, which permit early mobilisation to encourage enhanced recovery [2].

At the 'ripe age of fifty years', Ketamine is still considered a 'newcomer' in pain medicine. It is a phencyclidine derivative, introduced into medicine, as an anaesthetic, found to be a dissociative one [38]. The dissociative nature of Ketamine implies that the highest centre of the brain, the cortex, which normally controls the rest of the lower centres of the brain, can no longer do so, when Ketamine is administered [38], which then results in hallucinations and nightmares. This still remains a dreaded side effect of Ketamine, but can adequately be countered with benzodiazepines [15].

Hirota and Lambert [38] enumerated the analgesic and anaesthetic benefits of Ketamine,

- Improves opioid induced analgesia,
- Reduces opioid induced acute tolerance and spinal ischaemia,
- Anti-inflammatory and anti-tumour action,
- Avoids recall and awareness during general anaesthesia.

Persson [12] and Radvansky, et al. [11] found literature to show evidence that IV Ketamine peri-operatively does improve postoperative pain and reduce consumption of Morphine. A Cochrane review has been proposed by Brinck, et al. [39], with a plan to propose the use of IV Ketamine for the management of acute postoperative pain in adults to reduce opioid consumption and hasten discharge.

The use of Ketamine is one among the multimodal techniques recommended by the guideline by the ASA-TKAPM [5], which has been still growing at the National Health Service (NHS) [40]. Nygren, et al. [41], while formulating the ERAS protocols after rectal and pelvic surgeries, conclusively recommended the inclusion of epidural for such procedures, in addition to IV Lignocaine and /or TAP blocks. However, Joshi, et al. [42], in their systematic review of the methods of pain management after laparoscopic colorectal cases, did not find it was mandatory to provide neuraxial blocks to ensure adequate postoperative pain relief and found surgical wound infiltration to be adequate, supplemented with Paracetamol and NSAIDs, with or without IV Lignocaine. Hence, Ketamine could perhaps be considered for this purpose as well as an analgesic supplement.

The study by Kwok, et al. [18], specifically on laparoscopic gynaecological procedures, found pre-emptive IV Ketamine (0.15mg/kg) to improve postoperative pain scores and also reduce Morphine consumption, whilst Laskowski, et al. [13] reviewed different regimens of IV Ketamine administration for acute pain management, to find Ketamine to be useful in all regimens, irrespective of the time or dose (<0.5mg/kg to > 1mg/kg) used. The high level of evidence of these studies (2+ and 1++ respectively) would recommend the use of Ketamine for the ERAS protocol for acute pain after laparoscopic hysterectomy.

The studies on the use of IV Ketamine pre-emptively, 10-15 min. before the skin incision, were all RCTs, the level of evidence ranging from 2- to 2+. High pre-emptive doses of 0.5 mg/kg were used by Behdad, et al. [19] and Wang, et al. [26], with promising results, surprisingly with minimal side effects, one of them [19] using Midazolam to counter any side effects. Both these studies were on men only, where the gender differences in pain perception should be considered before transferring their results to a population of women for laparoscopic hysterectomy. However, in lower doses, although the IV (1 mg/kg) route reduced the pain score and the opioid consumption the best, the subcutaneous (SC)(1-2 mg/kg) route was found to be useful as well on patients of both genders who underwent laparoscopic cholecystectomy, by Safavi, et al. [3], which may be a more attractive option for our population on the NHS or where an IV access for some of our patients may be very difficult for various reasons. Acute pain management in opioid abusers was found to be better with the use of Ketamine to control pain and also reduce opioid consumption [20], with a dose as low as 0.1 mg/kg.

Additionally, the use of Remifentanil [20] for TIVA (total intravenous anaesthesia) is a new mode of anaesthesia the past two decades [43], which is being adapted to provide better haemodynamic stability and less respiratory depression, compared to the routine IV and inhalational induction and maintenance of anaesthesia. Remifentanil however, has been found to cause hyperalgesia and interestingly has been found to be countered by Ketamine [25]. Hence if Ketamine could be used to reduce the amount of Remifentanil used and also to counter the associated hyperalgesia, this would be added benefit and the idea would be welcome in the field of modern day anaesthesia.

As an adjuvant to opioid PCA, the qualitative review of Ketamine by Carnesten, et al. [25] did not show Ketamine to be useful for this purpose, but this review lacked statistical analysis, and hence is considered an expert opinion (level of evidence 3) only. The study by Lo, et al. [24] was specifically on abdominal hysterectomies and did not find any difference in the pain scores when Ketamine was added to the PCA, though used in the ratio of 1:1 with Morphine. This study, however, had a low power and poor rigour, due to the fact that parameters were evaluated only from the day after the surgical procedure, making the results less reliable. The subsequent two meta-analyses of RCTs on the use of Ketamine as an adjuvant to the opioid PCA by Ding, et al. [27] and Wang, et al. [26], showed supporting findings for our idea of including Ketamine for the acute pain management after laparoscopic hysterectomies, however, with a benefit of doubt as there was no focus on the type of surgery with either of these systematic reviews.

When Ketamine was used as an IV bolus and infusion by various regimens, Zakine, et al. [29] found both intraoperative infusion and infusion for 48hrs (both 2mcg/kg/min.) after an initial pre-incision bolus of 0.5mg/kg to be effective for acute pain management after major abdominal surgeries, a level of evidence (2+) (17) high enough and type of surgery focused on close enough, to enable us to transfer their results to the set of population for laparoscopic hysterectomies. A similarly high level of evidence was seen in the study by Parikh, et al. [31] who used a bolus (0.15mg/kg) postoperative which was followed by an infusion of 2mcg/kg/min. The lower dose as bolus here was perhaps sufficient as it was postoperatively, when there would less pain. The higher bolus dose of 0.5mg/kg by Zakine, et al. [29] and Lak, et al. [30] contributed to the intraoperative pain relief as well perhaps. Stessel, et al. [33] were unable to conclude their study to give us definitive outcome but their results showed a tendency to favour the use of Ketamine for postoperative pain relief. Jacobsohn, et al. [35] reviewed cases notes major surgeries done where Ketamine infusion postoperatively and when Ketamine was administered as an IV bolus postoperatively in the dose of 0.5mg/kg, alongside Paracetamol 1g, it was found to reduce pain and opioid consumption better, when compared when Tramadol was administered with Paracetamol.

The above literature review has shown that perioperative Ketamine is, indeed, effective in reducing postoperative pain opioid consumption, fulfilling the two main factors of ERAS protocol for pain relief to reduce side effects and therefore expedite discharge. Of the three regimens reviewed above, the pre-emptive use of IV Ketamine seems to have the best level of evidence to support its use for the major abdominal surgeries. The IV bolus and infusion regimen seems to have some good evidence as well. However, with the two studies on women [24] and on abdominal hysterectomies specifically [28] showing disappointing results with IV bolus and infusion, despite larger doses, more rigorous studies would need to be conducted to show us better evidence to the use Ketamine as a bolus and infusion. The studies on Ketamine with PCA were mainly systematic reviews and meta-analyses, with no focussed aim, which resulted in diverse results for each of the reviews and made it difficult to draw any definitive conclusions from their findings.

With the reduction of the NHS staffing, an administrative issue, it would indeed be, an immense challenge to implement the use of Ketamine as an adjunct with the Morphine PCA as it would warrant more intense ward-based monitoring of patient parameters. Hence it would perhaps be best to initiate the use of pre-emptive IV Ketamine as an element of a multimodal analgesia. This could then be followed by IV infusion regimens for short periods after surgery to enhance the acute pain relief maximally in the immediate postoperative periods when the degree of this kind of pain is at its maximum.

At the National Acute Pain Symposium (NAPS) 2016 at Chester, many speakers mentioned the use of Ketamine as a part of a multimodal strategy for the control of postoperative pain to support ERAS specifically, again pointing out that Ketamine could be used in various routes, however, many unlicensed. The intravenous route being licensed, Ketamine could be considered by this route for postoperative analgesia and more studies are required to implement the protocol on the NHS. There was one session at this NAPS meeting, exclusively on alternatives to opioids and regional techniques to ensure ERAS, when IV Ketamine for this purpose was discussed in detail, referring to some of the articles appraised above. One other factor repeatedly emphasised at this meet was the importance of patient education with subsequent anticipation of the degree of pain and potential pain relieving effects of the proposed analgesic methods would play a major role in the management of any kind of pain, acute or chronic. This was also discussed at the recent meet on 'Anaesthesia for Major Surgeries' at London (Oct. 2019).

CONCLUSION

In conclusion, to answer the aims of this review: critically evaluation of the evidence on the role of pre-emptive IV Ketamine for acute pain management after abdominal surgeries was performed, as was the evidence on the effectiveness and side effect profile of adding Ketamine to the Morphine PCA on postoperative pain and opioid consumption and also intravenous bolus Ketamine at induction followed by an IV infusion and its effect on postoperative pain, side effects and opioid consumption. A few of the studies in this review used Midazolam, which countered the side effects of hallucinations which are known to occur with Ketamine. As Midazolam is found to be good pre-medication to allay anxiety as well, we could perhaps suggest an addition of this to the protocol.

Although Ketamine was found to effective by all of the regimens examined, the pre-emptive route of administration was found to have the best of evidence for this purpose. An intraoperative infusion could be considered as well, with the concerned anaesthetist monitoring the patient throughout. The PCA and infusion regimens had good evidence as well, but would need adequate monitoring by qualified medical staff to make them safe, an administrative issue to be considered.

RECOMMENDATIONS

Keeping in mind all the requirements of the ERAS protocol, the following recommendations were made to the trust to consider promoting the use of pre-emptive IV Ketamine in a multimodal acute pain recipe for ERAS for laparoscopic hysterectomy as follows (Table 3).

Pre-operative administration of Midazolam and Gabapentin or Ketamine would be the first step for each of these protocols. Further recommendations are to follow a general standardised anaesthetic protocol, using it as a guide only, making changes to individual patient needs as essential and incorporating either of the above protocols, customised to individual patients. Allotting a section of the anaesthetic staff to cater to these ERAS needs for laparoscopic hysterectomy may a good idea, but the individual anaesthetists would need to be equally comfortable using the protocol to make the implementation of the idea more successful.

HH: first draft of literature review for dissertation, editing it to current format to conform to BJA criteria

SJ: Academic Supervisor, Guide for dissertation and editing it to current format

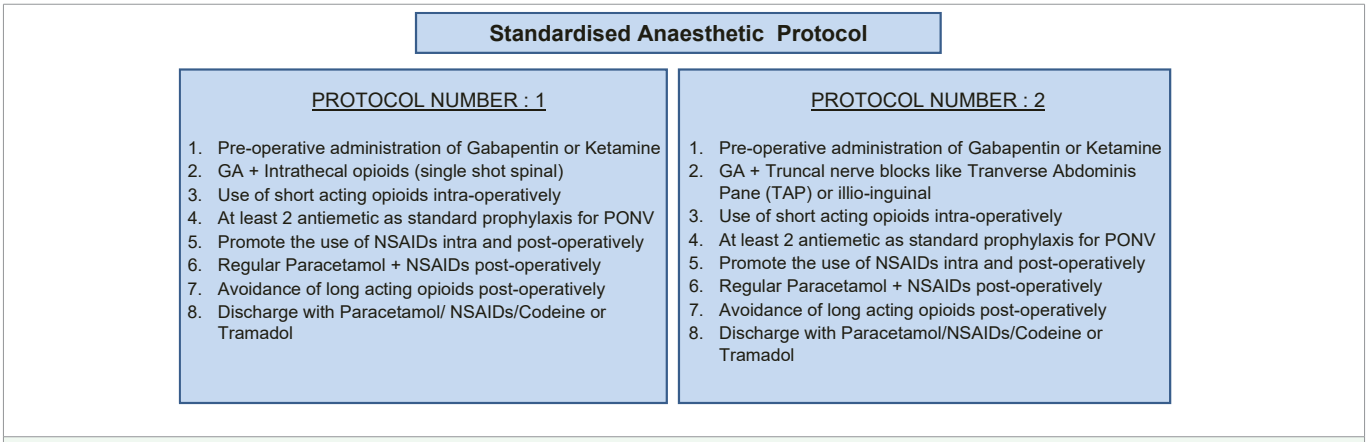

Figure 3: Recommendations.

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