

A comparative study to evaluate the analgesic effect and some vital signs effects of intravenous (Remifentanil - Morphine – Paracetamol)

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Key words: Pain management, intensive care unit, pain assessment, FLACC, morphine, remifentanil and Paracetamol infusion.

Abstract

Background: Pain is problematic in intensive care units (ICU) patients because produces adverse psychological and physiological response that includes increased heart rate, blood pressure, respiratory rate, neuroendocrine secretion and psychological distress. Opioid medications play role in pain control, but may cause a harmful effects on some vital signs. The primary goal of acute pain management are pain control and attenuation of the negative physiological and psychological consequences of unrelieved pain.

Objectives: To compares effect of Paracetamol, morphine & remifentanil and their activity as analgesic on some vital sings.

Patients & Methods: A prospective study was carried out in intensive care unit in AL Hussein medical city in Karbala during the period from first of November 2016 to the 28th of February 2017. 30 patients of both sex were involved in this study, aged from 18 to 65 years old. Eligible patients were randomly selected & classified to three groups A, B & C (10 patients each). Group A received Morphine intravenous bolus doses (1 mg/30 min), group B received Remifentanil infusion dose (0.1 mcg/ kg/ min), and group C received Paracetamol infusion dose (1g /6 hourly). Data including pain score, pulse rate & blood pressure, were recorded pre-treatment & then same data were taken & reported at 2 hours interval for 12 hours. The data were statistically analyzed by using T-test.

Results: It was found that Paracetamol has no significant effect on systolic, diastolic blood pressure and pulse rate (136 ± 4.65 , 75 ± 2.96 , 94 ± 4.39) respectively as it's mean \pm standard deviation values compared with pre-treatment values that represent control (138 ± 3.73 , 80 ± 2.96 , 99 ± 3.41), but with morphine group (124 ± 3.02 , 67 ± 3.20 , 89 ± 5.87) & remifentanil group (111 ± 5.64 , 61 ± 1.33 , 82 ± 5.27) respectively, in which they have shown significant effect on these vital signs (systolic, diastolic blood

pressure and pulse rate) compared with their pre-treatment values (138 ± 3.73 , 80 ± 2.96 , 99 ± 3.41). In addition, it was found that Paracetamol has less significant effect on pain score (face, legs, activity, cry, consolability) FLACC scale (4 ± 0.31) at (2,4,6,10,12) hours intervals compared with its pre-treatment value (5 ± 0.18) which means that paracetamol has lower analgesia than the two other drugs, morphine (2 ± 0.32) and remifentanyl (2 ± 0.26) respectively,

that have significant effect on FLACC scale at (2,4,6,8,10,12) hours intervals, compared with their pre-treatment values.

Conclusion: Paracetamol as analgesic has more vital signs stability compared with morphine & remifentanyl but it has less analgesic effects compared with the other two drugs.

دراسة مقارنة لتقييم تسكين الألم والتأثير على بعض العلامات الحيوية للأدوية الوريدية

(ريميفنتانيل - المورفين - البراسيتامول)

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الخلاصة

الكلمات التي من خلالها يمكن البحث بسهولة عن هذه الدراسة: معالجة الألم، وحدة العناية المركزة، تقييم الألم، الفلاك، المورفين، الريميفنتانيل و البراسيتامول الوريدي.

نبذة عن الدراسة: الألم يشكل مشكلة وعائق للمرضى في وحدة العناية المركزة لأنه يسبب تأثيرات ضارة نفسية وفسلجية تتضمن زيادة في نسبة دقات القلب، ضغط الدم، نسبة التنفس و إفرازات الصماء العصبية، وازعاج نفسي. علاجات الأفيون لها دور في السيطرة على الألم ولكن يمتلك تأثيرات ضارة على بعض الاشارات الحيوية. الهدف الاساسي من معالجة الألم الحاد هي السيطرة على الألم والتخفيف من العواقب النفسية والفسلجية الناتجة من الألم الغير قابل للشفاء.

أهداف الدراسة: مقارنة تأثير البراسيتامول، المورفين الريميفنتانيل وفعاليتهم كمسكن على بعض الاشارات الحيوية.

طرائق جمع المعلومات في هذه الدراسة: الدراسة تمت في وحدة العناية المركزة لمدينة الحسين (ع) الطبية في كربلاء خلال فترة تتراوح من 1 تشرين الثاني 2016 الى 28 شباط 2017. 30 مريض من كلا الجنسين شاركوا هذه الدراسة، اعمارهم تتراوح من 18 الى 65 سنة. المرضى المؤهلين تم اختيارهم عشوائيا وتم تقسيمهم الى ثلاث مجموعات أ، ب، ج (10 لكل مجموعة). مجموعة أ استلمت جرعات وريدية من المورفين (1 ملغم لكل 30 دقيقة)، مجموعة ب استلمت جرعات وريدية من الريميفنتانيل (1 ميكروغرام لكل كلغم في الدقيقة) ومجموعة ج استلمت جرعات وريدية من البراسيتامول (1 غم لكل 6 ساعات). النتائج تضمنت مقياس الألم (عبر استخدام معيار فلاك)، معدل النبض، ضغط الدم التقلصي والانبساطي، حيث سجلت النتائج عند اعطاء الدواء ثم تكرار جمعها كل 2 ساعة الى 12 ساعة. البيانات تم تحليلها احصائيا باستخدام فحص تي.

النتائج: لقد وجد أن البراسيتامول المعطى لمجموعة المرضى أ لا يمتلك اي تأثير واضح على ضغط الدم التقلصي والانبساطي و معدل سرعة النبض (136 ± 4.65 , 75 ± 2.96 , 94 ± 4.39) بالمقارنة مع مجموعة السيطرة (قبل اعطاء الدواء) والمتمثلة بالقيم التالية (138 ± 3.73 , 80 ± 2.96 , 99 ± 3.41)، لكن مع المورفين (111 ± 5.64 , 61 ± 3.02 , 89 ± 5.87) و الريميفنتانيل (124 ± 3.02 , 67 ± 3.20 , 89 ± 5.87)

($1.33, 82 \pm 5.27$) بالتناوب والمعطى للمجاميع الاخرى والتي لها تأثير واضح على هذه الاشارات الحيوية (الضغط التقلصي والانبساطي ومعدل سرعة النبض) مقارنة مع مجموعة السيطرة. بالإضافة الى ان البراسيتامول له تأثير قليل في تقليل الالم (4 ± 0.31) عند الفترات (2, 4, 6, 10) ساعة مقارنة مع مجموعة السيطرة (5 ± 0.18) وهذا يعني ان البراسيتامول يمتلك تأثير مسكن للألم اقل من الادوية الاخرى وهي المورفين (2 ± 0.32) والريميفنتانيل (2 ± 0.26) والتي تمتلك تأثير واضح على مقياس الالم عند الفترات (2, 4, 6, 8, 10, 12) ساعة مقارنة مع مجموعة السيطرة.

الاستنتاج: البراسيتامول كمسكن يعتبر اقل تأثيرا على العلامات الحيوية (الضغط التقلصي والانبساطي ومعدل سرعة النبض) مقارنة بالدوائن الاخرين الريميفنتانيل والمورفين وبذلك يكون البراسيتامول اكثر استقرارا من ناحية تأثيره على هذه العلامات الحيوية (الضغط الانبساطي والتقلصي ومعدل سرعة النبض). لكن البراسيتامول يمتلك تأثير مسكن للألم قليل مقارنة ببقية الادوية المذكورة.

Introduction

Pain is a complex sensation that different from person to person, even when the injury or cause seems the same. Pain that goes uncontrolled for a long time can alter one's mood and well-being^[1]. The nociceptors is main cause of pain which they are free nerve endings that answer to painful stimuli. Nociceptors are widely spread in human and animal body and can be found in skin, organ of motion such as periosteum, ligament, muscles, joint capsule, dental pulp and cornea of the eye. Also they are abundant in the meninges, peritoneum, pleura, and organ wall. They transport information to the brain when stimulated by thermal, mechanical, electrical, biological, and chemical stimuli which perception of pain take^[2]. Physiological responses stimulated by acute tissue injury to protect the body. When these responses continue uncontrolled that lead to adverse effects. More danger for such complications are occur with very young, very old and weak patients^[3].

Uncontrolled acute pain may be developed into chronic pain^[4]. According to one of studies that founded level of pain in patients with complexes diseases such as (liver failure, chronic obstructive pulmonary disease and cancer) determined level of pain in future. The pain later in life result from undertreated pain early in life^[5].

The pain sufferers are unable to do daily living activity such as (hobbies, relationships, work, sex) with uncontrolled of pain in addition to adverse psychological consequences^[6]. Patients in unmanaged pain may fell with depression, anxiety, anger, anger or cognitive dysfunction, These complications are occur in patients with chronic pain^[7].

Opioids are the main medications for treatment pain in critically ill patients due to of efficacy, sedative and anxiolytic properties, and they can be administered by different routes. Morphine sulfate is the most frequently used opioid in the ICU and has been traditionally a first-line opioid for the treatment of severe pain. Continuous IV morphine can be administered with an initial 2–5 mg bolus dose followed by 1 mg/h^[8]. According some studies that founded with remifentanil use to need a shorter

duration for mechanical ventilation and faster ICU patients discharge compared with other opioid^{[9][10]}.

Paracetamol was approved for intravenous use in 2010 and is commonly administered for the short-term treatment of mild to moderate pain and febrile critically ill patients with infection. It differs from the available opioids and NSAIDs, since paracetamol does not cause of nausea, vomiting, and respiratory depression that can associated with opioids, or the platelet dysfunction, gastritis, and renal toxicity that are occur with NSAIDs^[11].

Aim of the study:

To compare effect of Paracetamol on some vital sings (SBP, DBP, PR) and its activity as analgesic compared with morphine & remifentanil.

Patients & Method :

A prospective study was carried out in intensive care unit in AL Hussein medical city in Karbala during the period from first of November 2016 to the 28Th of February 2017, 30 patients were included.

Exclusion criteria:

- Age less than 18 & more than 65
- Allergy to the study drug
- History of chronic or acute liver disease
- History of chronic alcohol intake.
- Acute or chronic renal failure.
- Hemodynamic instability (as systolic blood pressure < 90 mmHg inspite for use vasopressor).

Eligible patients were randomly selected & classified to three groups A, B & C (10 each group). Group A received Morphine intravenous bolus doses (1 mg/ 30 min), group B received Remifentanil infusion dose (0.1 mcg/ kg/ min) and group C received Paracetamol infusion dose (1g /6 hourly) ^[12].

- number of patients in the first group (group A which is morphine group) is ten patients and male to female ratio is 5/5 with an average age of 38.1 ± 12.13 .
- Regarding group B (Remfentanil group), male to female ratio M/F IS 5/5 with an average age of 38.1 ± 12.13 .
- Regarding group C (paracetamol group), male to female ratio (M/F) is 3/7 with an average age of 41.4 ± 12.89 .

Data including pain score (FLACC), pulse rate & blood pressure, were recorded at immediate post-drug administration & then same data were taken & reported at 2 hours interval for 12 hours.

Results

By applying the SPSS using T-test analysis, table 1; showing values as mean \pm standard deviation of (SBP,DBP,PR & FLACC) of paracetamol at pre-treatment and at post-treatment (from 2 to 12) hour. When compared paracetamol with pre-treatment, found its insignificant effect on SBP,DBP, FLACC at (2,4,6,8,10,12) hr. But it's effect on pulse rate different which it's significant effect at (4 & 6) hr and insignificant effect at (2,8,10,12) hr.

Table 2; showing values as mean \pm standard deviation of (SBP,DBP,PR & FLACC) of remifentanyl at pre-treatment and at post-treatment (from 2 to 12) hour. When compared remifentanyl with pre-treatment, found its significant effect on DBP, PR, FLACC at (2,4,6,8,10,12) hr. and significant effect on SBP at (4,6,8,10,12) hr. except 2 hr.

Table 3; showing values as mean \pm standard deviation of (SBP,DBP,PR & FLACC) of morphine at pre-treatment and at post-treatment (from 2 to 12) hour. When compared morphine with pre-treatment, found its significant effect on SBP at (6,8,10,12) hr except (2 & 4) hr. Its significant effect on DBP at (4,6,8,10,12) hr except 2 hr. Its insignificant effect on PR, but its significant effect on FLACC at (2,4,6,8,10,12) hr.

Table 4; showing values as mean \pm standard deviation of (SBP,DBP,PR & FLACC) at pre-treatment and each drug (paracetamol, morphine and remifentanyl), which found the paracetamol has insignificant effect on these parameters (SBP,DBP,PR & FLACC) compared with pre-treatment.

But morphine and remifentanyl have significant effect on these parameters (SBP,DBP,PR & FLACC) compared with pre-treatment.

When comparison between the effects of all these three drugs on (SBP,DBP,PR & FLACC), it found that paracetamol is much far more safe on these vital signs (DBP, SBP, PR) compared with the other two drugs which they significantly influenced those three vital signs (SBP, DBP, PR). However, the paracetamol, as shown in table 4, its effects on FLACC scale is not significant which reflects that it has poor or less analgesia when compared with morphine and remifentanyl.

Table (1): Shows the effects of paracetamol on (systolic & diastolic) blood pressure, pulse rate and FLACC value. * mean $P \leq 0.05$.

Hours Parameters	Pre- treatment	2hr	4hr	6hr	8hr	10hr	12hr
SBP	134± 5.36	131± 4.52	129± 5.02	130± 5.63	129± 4.80	136± 5.46	136± 4.65
DBP	69± 2.92	70± 2.40	67± 2.12	66± 2.47	70± 2.73	75± 3.02	75± 3.20
PR	87± 5.37	86± 4.16	88± 2.83*	87± 4.25*	89± 5.07	93± 4.03	94± 4.39
FLACC	5.4± 0.34	4.7± 0.26	4.3± 0.21	4.1± 0.34	5± 0.29	5± 0.39	4.9± 0.31

Table (2): Shows the effects of remifentanyl on (systolic & diastolic) blood pressure, pulse rate and FLACC value. * mean $P \leq 0.05$.

Hours Parameters	Pre- treatment	2hr	4hr	6hr	8hr	10hr	12hr
SBP	136± 8.05	119± 8.22	115± 7.65*	114± 6.74*	115± 5.77*	116± 4.70*	111± 5.64*
DBP	88± 5.73	71± 4.98*	65± 3.28*	64± 1.52*	60± 1.90*	62± 1.70*	61± 1.64*
PR	110± 4.94	83± 5.25*	83± 4.02*	81± 4.93*	82± 4.51*	83± 5.05*	82± 5.27*
FLACC	5± 0.30	3± 0.26*	3± 0.21*	2± 0.22*	2± 0.20*	2± 0.10*	2± 0.26*

Table(3). Shows the effects of morphine on (systolic & diastolic) blood pressure, pulse rate and FLACC value. * mean $P \leq 0.05$.

Hours Parameters	Pre- treatment	2hr	4hr	6hr	8hr	10hr	12hr
SBP	145± 5.82	136± 5.68	133± 4.22	129± 4.52*	125± 3.90*	123± 4.72*	124± 3.02*
DBP	84± 4.76	78± 4.60	73± 4.48*	73± 2.98*	71± 3.80*	65± 2.16*	76± 1.33*
PR	100± 5.66	92± 5.66	93± 6.64	91± 5.62	90± 5.28	90± 3.95	89± 5.87
FLACC	5± 0.33	3± 0.26*	3± 0.38*	2± 0.27*	2± 0.21*	2± 0.26*	2± 0.32*

Table (4). Shows the different in each drug effects on (systolic & diastolic) blood pressure, pulse rate and FLACC value. * mean $P \leq 0.05$.

Parameters Drugs	SBP	DBP	PR	FLACC
Pre-treatment	138 ± 3.73	80 ± 2.96	99 ± 3.41	5 ± 0.18
Paracetamol	136 ± 4.65	75 ± 2.96	94 ± 4.39	4 ± 0.31
Morphine	124 ± 3.02*	67 ± 3.20*	89 ± 5.87	2 ± 0.32*
Remefentanil	111 ± 5.64*	61 ± 1.33*	82 ± 5.27*	2 ± 0.26*

Discussion

This study was found that paracetamol has insignificant effects on (SBP), (DBP), (PR) and (FLACC) were obtained which P value more than 0.05 compared with the other two drugs (Remifentanil and Morphine) which they have excellent analgesia and they made critical change in flacc scale value pre and post administration, in addition, they have had harmful effects on the vital hemodynamic stability which P value less than 0.05. These advantages and disadvantages of each drug make it difficult to choose or point to the drug easily because every drug will suit its appropriate case or situation so there is contraversality in this regard and many of

health care centers and research studies have different erratic opinions about what drug to choose between these drugs. These results showing a comparison between the effects of all these three drugs on DBP, SBP, PR, and FLACC scale and it is obvious that the paracetamol is much far more safe on these vital signs (DBP, SBP, PR) compared with the other two drugs which they significantly influenced those three vital signs (DBP, SBP, PR). However, the paracetamol effects on FLACC scale is not significant which reflects that it has poor or less analgesia when compared with remifentanyl and morphine.

Tachycardia and hypotension occur through general anaesthesia with use of 0.6 mg/kg morphine^[13], where morphine does not affect at all on the hemodynamics of healthy volunteers^[14]. The vasodilatation induced by 15 mg intravenous morphine is possibly preceded by ^[15]. By mediation the release of catecholamines therefore morphine can be a chronotropic effect ^{[16][17]}.

In a study of remifentanyl effect on cardiovascular system, occur transient bradycardia for four patients, without need to treatment^[18].

Other studies in use of remifentanyl with lack of vagolytic drug shown occur of bradycardia and hypotension^[19]. Use of remifentanyl and alfentanil through anaesthesia and through orotracheal intubation was effective in pressor response attenuation with hypertensive and elderly patients^[20,21].

Modern studies in use of intravenous paracetamol for critical ill patients with transient hypotension^[22-29]. In 2010 which studies examined the haemodynamic effect for use formulation of intravenous paracetamol^[24].

Our study showed a significant decrease in systolic blood pressure (SBP) with intravenous paracetamol use. Recently, Needleman founded the safety of rapid infusion of intravenous paracetamol use^[25]. In a retrospective chart review, was found significant decreased in (systolic & diastolic) blood pressure and mean arterial pressure with intravenous paracetamol use. The study methodology needed monitoring of these variables in 2 minute intervals at infusion and up until 5 minutes after infusion. The author did not limit when rapid infusion may be changed haemodynamics after this short period of monitoring .

When collection the data of this study the instrument was progressed, so it was being used for the first time. In addition, the indicators reported can be related to other signs of anxiety but they are not specific to pain in critical ill patients^[30]. We must suppose that patients can exam pain and that they worth it to have their pain estimate and removed^[31].

Conclusion& Recommendation

In our study we have compared the efficacy of morphine, remifentanyl & paracetamol, given in preventing pain. It has been concluded from this study that the paracetamol is

more vital signs stable compared with morphine & remifentanyl and also this study mention to that the paracetamol is weak analgesic comparing with the other two drugs. In order to get more accurate results, we recommended studying the analgesic activity of more drugs, over longer period, increased the dose and involving more patients than our study.

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