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"Opioid creep" is real and may be the cause of "fluid creep"

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Abstract

Recent studies have shown that burn patients receive larger volumes of fluids than predicted by the Baxter formula and the reason for this is unclear. One potential reason is that increased analgesics are used which could blunt the response to fluid resuscitation. The purpose of this study was to compare the administration of opioid agonists in patients treated at a single burn center in the 1970s and in the year 2000. We performed a retrospective chart review comparing two matched cohorts. Group I consisted of 11 patients admitted between 1975 and 1978. Group II consisted of 11 patients admitted in 2000 matched for age, sex and %TBSA. Patients in Group II received a significantly higher mean opioid equivalent than those in Group I (26.5 ± 12.3 versus 3.9 ± 2.2 in the first 24 h, $P < 0.001$). In addition, in Group II, a larger variety and combination of opioid agonists were used. This review demonstrates a significant increase from the 1970s to 2000 in the type, dose prescribed and dose delivered of opioid agonists. Along with "fluid creep", we have also increased our use of opioid agonists or "opioid creep". Higher doses of opioid agonists may have hemodynamic consequences, which may contribute to the increased fluid volumes.

Keywords: Burn; Opioid; Analgesics; Pain

1. Introduction

A major burn injury results in hypovolemia induced burn shock, hypoxia and severe pain [1]. The acute post-burn period in the first 48–72 h is marked by cardiovascular instability due to this hypovolemia from fluid shift and loss [2,3]. Though treatment of major thermal injuries has evolved over the last 30 years, the focus of care during this acute period remains airway management, intravascular volume resuscitation and pain control.

In 1968, Charles Baxter first described using 3.7–4.3 mL/kg per percentage total body surface burned area (%TBSA) of lactated Ringers as a guideline for effective fluid resuscitation following burn injury [4–12]. In 2000, Engrav et al. [13] reported that 58% of patients admitted that year to six burn centers in the United States received more than 4.3 mL/kg per %TBSA. This phenomenon of providing excessive fluid resuscitation volumes has been termed "fluid creep" by Pruitt [14]. Although complications from excessive fluids have not been clearly established in burn patients, it is known that large fluid volumes contribute to abdominal and compartment syndromes and to pulmonary complications [15–19].

In 1973, Marks and Sachar [20] reported that house staff physicians underprescribe medication for acute burn pain, and to compound the issue, only a fraction of the analgesics prescribed were delivered. In the subsequent 30 years, many other authors have also described inadequate treatment of acute pain [21–25]. Just as we have previously reported that burn patients receive significantly larger volumes for fluid resuscitation [26], we have also observed that patients receive

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larger doses of opioid agonists during the acute 48–72 h period after a major burn. Perhaps we have responded to reports of inadequate treatment with the prescription and delivery of increasing doses of opioid agonists. Thus, along with "fluid creep", we may have also increased our use of opioid agonists, a phenomenon we have now termed, "opioid creep". Higher doses of opioid agonists are not likely without hemodynamic consequence [27,28]. These higher doses of opioids likely contribute to hypotension and therefore may increase fluid needs in the period of acute burn shock.

The purpose of this study was to compare opioid agonist use between two matched cohorts of patients treated at two distinct time periods (1970s and 2000) during the acute period after a major burn injury. We hypothesized that there was a significant increase in opioid use.

2. Methods

Following University of Washington Human Subjects Committee approval, we retrospectively reviewed records of two cohorts of patients admitted to the University of Washington Burn Center at Harborview Medical Center with a major burn, as defined by MacLennan et al. [1] Group I consisted of 11 patients admitted to this burn center between 1975 and 1978. These patients were selected because historical charts were complete and available for review. Group II consisted of 11 patients matched for age and %TBSA (partial and full-thickness burns) admitted to this burn center in 2000. Demographic and clinical data and several independent variables were collected for each patient. Our outcomes of interest were type of opioid agonist delivered, total amount of opioid agonist prescribed for pro re nata (PRN) pain control, total amount of opioid agonist delivered in each 24 h period for the first 72 h after hospitalization and the correlation of opioid equivalents and fluid volumes. Total amounts of sedative-hypnotic and paralytic medications were also collected for each 24 h period.

The treating physician determined which opioid agonists and what dose ranges should be administered. Opioid agonists include morphine sulfate, meperidine, codeine, oxycodone, hydromorphine, methadone, fentanyl and sufentanil [29] Choice of medication was individualized to the patient's condition (i.e. ability to take medication by mouth) and physician preference. Nursing staff delivered a dose based on their assessment of the patient's level of pain and within the prescription limitations. For purposes of data analysis, the diverse types and doses of opioid agonists delivered were converted to opioid equivalents (OE) [29,30] based on American Pain Society standard equivalency recommendations [31]. One opioid equivalent theoretically is equipotent in analgesic effects to morphine 10 mg administered intravenously (IV) [32].

The Mann–Whitney *U*-test was used to test for potential differences between continuous variables and the Chi-square or Fisher's (two-tailed) exact test was used to test for potential differences in proportions between categorical variables of the two groups. The Spearman test was used evaluate for correlation between opioid equivalents and fluids administered. Results are reported as mean ± standard deviation. Statistical analyses were performed using Stata 6.0 software (StataCorp, College Station, TX, 1999) and SPSS 11.0.1 (SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics

The demographics and clinical characteristics of Groups I and II were similar except that fluids administered to Group II significantly ($P < 0.001$) exceeded those delivered to Group I (Table 1). Although two more patients in Group II than Group I suffered smoke inhalation, their fluid requirements did not differ significantly from those without smoke inhalation.

3.2. Types of opioid agonists

The diversity and number of opioid agonists administered increased from the 1970s to 2000 (Table 2). In Group I, a single medication for pain, morphine administered IV, was delivered to nine patients while the other patients received a combination of two opioid agonists. In Group II, the pattern was the opposite with only two patients receiving a single opioid agonist, while the remaining nine patients received a combination of up to four agonists.

Table 1
Demographics and clinical characteristics

	Group I	Group II	*P*
Age (year)	35 ± 15	33 ± 13	NS
Range	16–66	13–56	NS
Male sex—no. (%)	8 (72%)	8 (72%)	NS
Weight (kg)	81 ± 21	74 ± 20	NS
Range	54–117	44–103	NS
%TBSA: 2nd + 3rd degree	58 ± 17	48 ± 15	NS
Range	22–85	27–76	NS
Type of burn			NS
Flame—no. (%)	9 (82%)	11 (100%)	NS
Tar/grease—no. (%)	2 (18%)	0 (0%)	NS
Smoke inhalation injury - no. (%)	3 (27%)	5 (45%)	NS
Intubated—no. (%)	6 (55%)	9 (82%)	NS
History of psychiatric diagnosis or positive drug or alcohol screen (%)	4 (36%)	4 (36%)	NS
Total fluids first 24 h (cc/kg per %TBSA)	3.6 ± 1.1	8.0 ± 2.5	<0.001

NS: not significant.

Table 2
Comparison of opioid agonists delivered in the first 72 h

Opioid agonist delivered	Group I	Group II
Morphine	9	0
Fentanyl	0	2
Morphine + hydromorphone	1	0
Morphine + meperidine	1	0
Fentanyl + morphine	0	5
Fentanyl + morphine + oxycodone	0	1
Fentanyl + morphine + methadone	0	1
Fentanyl + oxydodone + methadone	0	1
Fentanyl + morphine + oxycodone + hydromorphone	0	1

3.3. Prescribed opioid agonists

The maximum prescribed OE increased significantly between the 1970s and 2000 for the first, second and third 24-h period after admission (Fig. 1). For Group I, all 11 patients had opioid agonists prescribed as PRN baseline pain or wound care and the average maximum prescribed PRN OE for each of the first three 24 h periods was 7.2 ± 2.9. For Group II, 8 of 11 patients had opioid agonist drip orders to "titrate to comfort" for baseline pain. It was not possible to calculate a maximum prescribed PRN OE for these orders. In addition to these drip orders, all 11 patients from Group II also had PRN opioid agonist orders for baseline pain or wound care with an average maximum prescribed PRN OE of 34 ± 25, 33 ± 25 and 32 ± 25 for each of the first three 24 h periods, respectively. Excluding the drip orders, patients from Group II still had a significantly greater median OE available as additional PRN orders when compared to the median of the maximum prescribed PRN OE available to Group I for each of the first three 24 h periods after admission ($P = 0.001$ for each 24 h period).

3.4. Delivered opioid agonists

The dose of opioid agonist delivered to patients is presented in Table 3. The total OE delivered to patients from Group II was greater than that delivered to patients from Group I in each of the first three 24 h periods after admission (Fig. 2). These differences were significantly greater than would be expected by chance alone ($P < 0.001$ for each 24 h period).

Table 3
Comparison between Groups I and II of maximum delivered PRN OE and OE delivered in each of the first three 24 h periods

	OE	μ/kg/h	mg/kg
Group I opioid agonist delivered			
First 24 h	3.9 ± 2.2	20.1 ± 10.4	0.5 ± 0.3
Second 24 h	3.3 ± 1.8	17.5 ± 11.0	0.4 ± 0.3
Third 24 h	3.1 ± 1.3	15.0 ± 8.2	0.2 ± 0.4
Group II opioid agonist delivered			
First 24 h	26.5 ± 12.3	163.5 ± 97.1	3.9 ± 2.3
Second 24 h	24.0 ± 11.5	145.6 ± 78.5	3.5 ± 1.9
Third 24 h	27.6 ± 21.9	164.5 ± 137.4	3.9 ± 3.3

3.5. Delivered versus prescribed opioid agonists

Consistently, patients from Group I received significantly less median OE than the median of the maximum prescribed PRN OE available in each of the first three 24 h periods (3.9 ± 2.2 versus 7.2 ± 2.9, $P < 0.05$; 3.3 ± 1.8 versus 7.2 ± 2.9, $P < 0.01$; 3.1 ± 1.3 versus 7.2 ± 2.9, $P < 0.01$, respectively) (Fig. 3a). This was not the case for Group II (Fig. 3b). Most of the patients from Group II had opioid agonist drips titrated for comfort with no maximum OE for these drip orders. Excluding the OE available by these drips, patients from Group II were delivered a median OE that was not different from the median of the maximum prescribed PRN OE available in each of the first three 24 h periods (27 ± 12 versus 34 ± 25, $P = 0.83$, 24 ± 12 versus 33 ± 25, $P = 0.52$, 28 ± 22 versus, 32 ± 25, $P = 0.28$) (Fig. 3c).

3.6. Correlation of opioid equivalents and fluids

The Spearman correlation for opioid equivalents and fluids administered (cc/kg per %TBSA) in the first 24 h is 0.6 ($P < 0.01$) (Fig. 4), which denotes a relatively strong linear association.

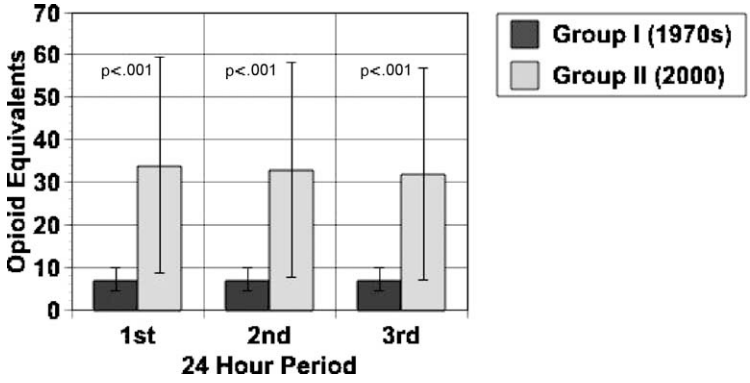

Fig. 1. Maximum prescribed PRN opioid equivalents during the two periods.

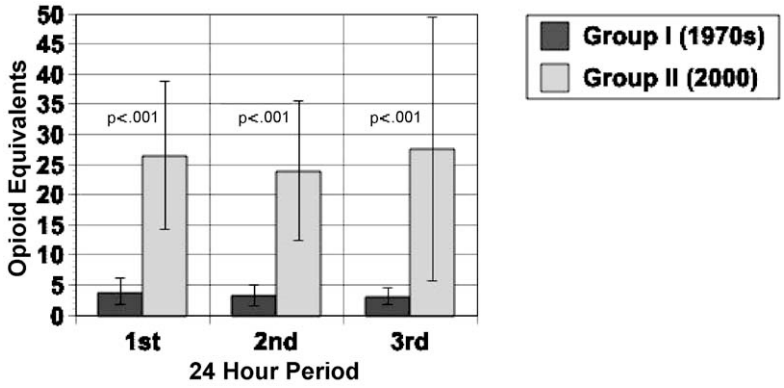

Fig. 2. Opioid equivalents delivered.

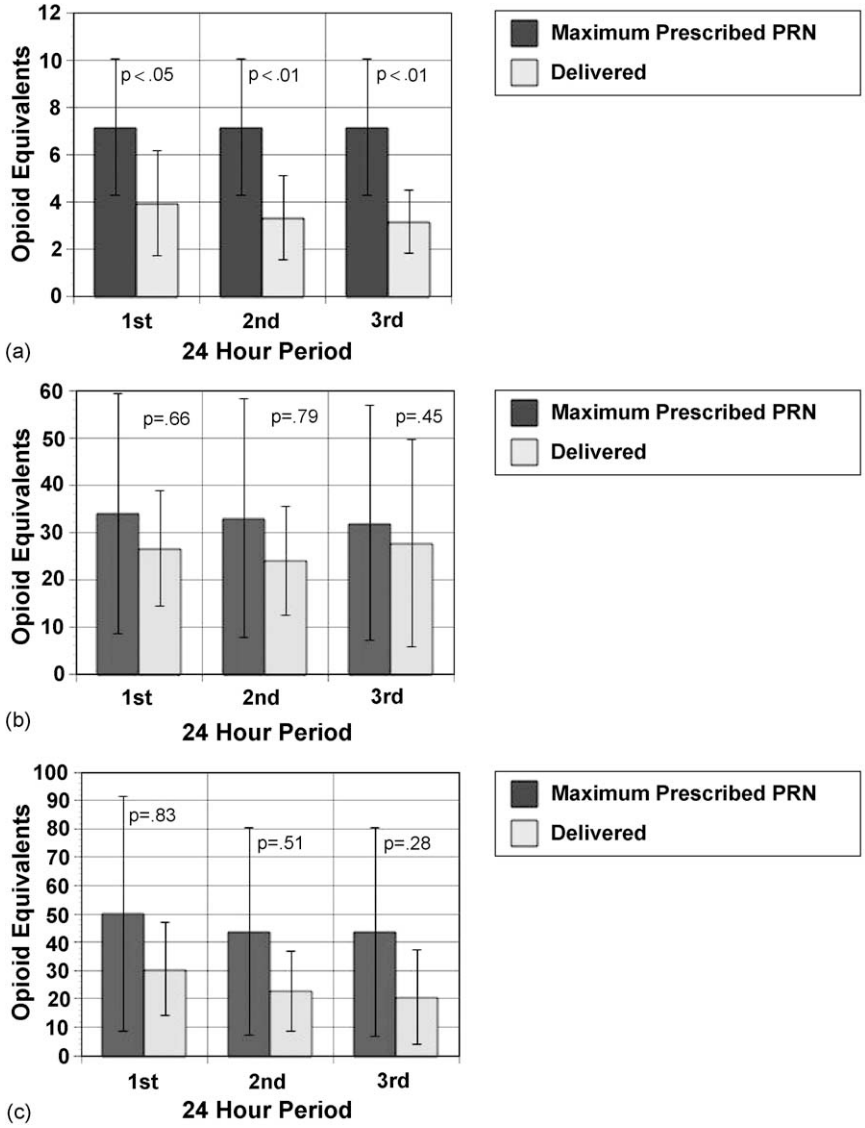

Fig. 3. (a) Comparison of prescribed and delivered opioids in Group I (1970s). (b) Comparison of prescribed and delivered opioids in Group II (2000). (c) Comparison of prescribed and delivered opioids in Group II (2000) patients without opioid drips.

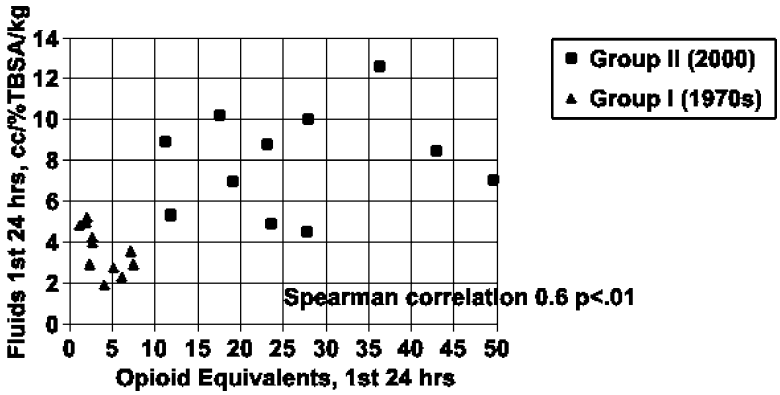

Fig. 4. Correlation of fluids and opioid equivalents.

3.7. Type and dose of sedative-hypnotic and paralytic drugs

The number of patients who received a sedative-hypnotic drug increased from the 1970s to 2000. In Group I, one patient received a paralytic drug, pancuronium. Sedative-hypnotic drugs were given to 5 of 11 patients with two patients receiving diazepam, a long-acting benzodiazepine, two received hydroxyzine pamoate, a long-acting histamine receptor antagonist with significant central nervous system depressant activity, and one received chloral hydrate, a nonselective sedative-hypnotic drug. The average dose of midazolam delivered in each of the first three 24 h periods was 9.3 ± 2.5, 18.5 ± 2.1 and 0 mg, respectively. In Group II, one patient received pancuronium. Sedative-hypnotic drugs were given to 9 of 11 patients with 3 receiving midazolam, a short-acting benzodiazepine; 3 received lorazepam, an intermediate duration benzodiazepine, and 3 received both midazolam and lorazepam. Drip orders to "titrate to comfort" were written for 8 of the 11 patients. The average dose of midazolam delivered in each of the first three 24 h periods was 49.0 ± 60.8, 106.0 ± 100.0 and 159.0 ± 173.4 mg, while that of lorazepam was 43.8 ± 44.5, 61.5 ± 75.5 and 53.9 ± 63.8 mg, respectively (Table 4).

Table 4
Comparison of sedative-hypnotic and paralytic drugs delivered in the first 72 h

Sedative-hypnotic/paralytic drug delivered	Group I	Group II
Pancuronium	1	1
Diazepam	2	0
Hydroxyzine pamoate	2	0
Chloral hydrate	1	0
Midazolam	0	3
Lorazepam	0	3
Midazolam and lorazepam	0	3
Drip order with "titrate to comfort"	0	8

3.8. Psychiatric disorders and positive drug or alcohol screens

Four patients in each group were noted to have a history of psychiatric disorder or positive drug or alcohol screens. In Group I the mean opioid equivalents for those with and without these conditions was 4.3±2.9 and 3.7±2.0, respectively. In Group II, the mean opioid equivalents for those with and without these findings were 25.6 ± 16.7 and 27.0 ± 10.5, respectively. There was no statistical difference ($P > 0.05$).

4. Discussion

Treatment of major burn injury in the acute period remains airway management, volume resuscitation and pain control. However, it appears that over the last 30 years, care may have changed such that we now see a pattern of increased fluid resuscitation volumes (fluid creep) as well as increased opioid analgesic administration (opioid creep). One explanation for fluid creep may be the increasing doses of opioid agonists that patients receive. Our study confirmed our hypothesis by showing a significant increase from the 1970s to the year 2000 in the type, dose prescribed and dose delivered of opioid agonists between two similar groups of patients with major burn injury during the acute resuscitation period.

4.1. Prescribed opioid agonists

In Group I, most patients received a single medication for pain, while in Group II, patients were often given some combination of up to four different opioid agonists. Latarjet and Choinere [33] recommends avoiding polypharmacy to better understand the pharmacologic properties, dose effect relationship and efficacy/safety ratio. It is possible that we need to limit the diversity of opioid agonists as this could lead to lower doses with better pain control.

Prescription and administration of pain medications are primarily based on the assessments and the impressions of

the treating physician and nurse [33]. However, physician and nurse impression of burn patient pain have been studied and are often unreliable [21,34–37]. It is possible that we now prescribe and deliver doses of opioid agonists that are, at times, in excess of that needed for adequate pain relief.

4.2. Delivered opioid agonists

Patients from Group II were delivered significantly more OE than those from Group I. Additionally, significantly less OE were delivered than were available by prescription for Group I, while there was no difference in the amount of OE delivered to patients from Group II when compared to that available by prescription. Latarjet and Choinière [33] state that the initial stages of burn pain have clearcut features including precise description, obvious cause and a reliable dose–effect pharmacological relationship. However, determining a reliable dose–effect relationship for opioid agonists may not be so straight forward. Published recommendations for pain treatment have increased over the last 30 years and many authors have emphasized the need for more aggressive analgesic intervention for burn injury [24,38]. When the OE delivered to patients in our study are compared to the recommendations of others, it appears that we used lower doses for Group I and higher doses for Group II than many of the published recommendations [23,24,33,39–41]. Our own center has reported that insufficient analgesics are often prescribed to burn patients, and even when adequate doses are ordered, nurses in the past have delivered less than half of the prescribed daily dose [42]. With many reports of undermedication, including that from our own institution, we may have been encouraged to prescribe and deliver increasingly higher doses of opioid agonists.

Indeed, patients with burns require high doses of opioid agonists for pain relief, but this delivery is not without consequences. The clinical course of burns is marked by hypotension and total body instability due to intravascular volume depletion for the first 24–48 h after a burn. The administration of high doses of opioid agonists may further alter the hemodynamics of burn patients by potentiating this instability and blunting the response to fluid resuscitation [27,28]. With these changes in hemodynamics, physicians may respond with increased volume resuscitation. Volume resuscitation has increased over the same 30 year period that we have observed an increase in OE. The hemodynamic effects of higher doses of opioid agonists may lead to the increased volume resuscitation in the acute period or “fluid creep” as suggested by the correlation of 0.6. During a time of cardiovascular chaos in the acute period, balance must be achieved between the effects on pain control and the potential for exacerbation of hemodyamic instabilty caused by high doses of opioid agonists. The scatter plot and correlation (Fig. 4) suggest that administering more than 10 opioid equivalents in the first 24-h period may be unwise.

In addition to hemodynamic alterations, the pharmacokinetics of medications change during this acute phase of major burn injury and may be further altered with the larger volumes of resuscitation now used [29,43]. Pharmacokinetic parameters such as absorption, bioavailability, protein binding, volume of distribution and clearance of medications change [44]. The extent of these changes depends on the magnitude of injury and the time between injury and drug administration [45]. The effect of burn on renal clearance is debated in the literature. Morphine is largely eliminated by hepatic metabolism and its principal metabolites by renal excretion [46]. Herman found the elimination half-life of morphine oral solution was similar between patients with and without burns though suggests that morphine is cleared more rapidly in patients with burns [47]. Furman found that morphine elimination is diminished and reported a decrease in the volume of distribution and clearance and an increase in the elimination half-life of morphine in the acute period after major burn injury [48]. Perry found that morphine is cleared by normal metabolic pathways in patients with burns and pharmacokinetics are similar in patients burned and not burned, though this study was not in the acute period [49]. Perreault also states that the effects of major burn injury on metabolism and organ flow do not modify clearance of morphine and its metabolites [50].

4.3. Psychiatric disorders or positive drug or alcohol screens

Perry et al. [24] reported 40% of a cohort of patients had a history of drug abuse, alcoholism, or psychiatric hospitalization though these patients did not report a significant difference in amount of pain or differ in the amount of pain medication received. While patients with this history might require larger doses of opioids due to tolerance, we did not find a difference between patients with or without this history in either Groups I or II.

4.4. Sedative-hypnotic drugs

In addition to higher doses of opioid agonists, we used benzodiazepines more frequently and in much higher doses in 2000 when compared to the 1970s. Benzodiazepines are used for sedation and anxiety. Because acute pain is exacerbated by anxiety, benzodiazepines can reduce pain when combined with opioid agonists [51]. Despite the use of drips and high doses of benzodiazepines for patients in Group II, these patients still received much larger doses of opioid agonists. Additionally, benzodiazepines, like opioid agonists, decrease blood pressure and increase heart rate. Large doses of benzodiazepines, therefore, may contribute to excessive volume resuscitation in the acute period after major thermal injury. With larger volumes of resuscitation, plasma albumin concentrations decrease and binding of drugs such as benzodiazepines is decreased, resulting in an increase in the free fraction and thus a larger volume of distribution for the

drug [52]. This then results in a need for even larger doses of benzodiazepines.

4.5. Patient self-reports of pain

In the 1970s, patient self-reports of pain were not consistently documented. Therefore, a comparison of patient self-reports of pain is not possible.

4.6. Future directions

We are obligated to evaluate further this growth in use of opioid agonists for burn pain treatment. Similar comparisons should be done at other burn centers to see if the same trend applies. Poor response of opioid agonists to pain control should not simply mean giving higher and higher doses, but instead, requires further investigation. Non-pharmacological methods of pain control should also be utilized. Non-opioid agonist approaches to burn pain such as provider and patient education, behavioral interventions, family presence, hypnosis, and virtual reality have been described [37,51]. Furthermore, the burn team must investigate the relationship between opioids, benzodiazepines and increased fluid volumes.

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References

[1] MacLennan N, Heimbach DM, Cullen BF. Anesthesia for major thermal injury. Anesthesiology 1998;89:749–70.
[2] Gueugniaud PY, Carsin H, Bertin-Maghit M, Petit P. Current advances in the initial management of major thermal burns. Intensive Care Med 2000;26:848–56.
[3] Miller JG, Bunting P, Burd DA, Edwards JD. Early cardiorespiratory patterns in patients with major burns and pulmonary insufficiency. Burns 1994;20:542–6.
[4] Baxter C. Fluid volume and electrolyte changes of the early postburn period. Clin Plast Surg 1974;1:693–709.
[5] Baxter C. Fluid resuscitation, burns percentage, and physiologic age. J Trauma 1979;19(Suppl):864–6.
[6] Baxter C. Guidelines for fluid resuscitation. J Trauma 1981;21 (Suppl):687–9.
[7] Baxter C, Shires T. Physiologic response to crystalloid resuscitation in severe burns. Ann N Y Acad Sci 1968;150:874–93.
[8] Baxter CR. Early resuscitation of patients with burns. In: Welch CE, editor. Advances in Surgery, vol. 4. Chicago: Year Book Medical Publishers; 1970. p. 308–24.
[9] Baxter CR. Crystalloid Resuscitation of Burn Shock. In: Polk HC, Jr., Stone HH, editors. Contemporary Burn Management Boston: Little, Brown and Company, 1971:7–32.
[10] Baxter CR. Response to initial fluid and electrolyte therapy of burn shock. In: Lynch JB, Lewis SR, editors. Symposium on the Treatment of Burns Saint Louis: C. V. Mosby Company; 1973. p. 42–8.
[11] Baxter CR. Problems and complications of burn shock resuscitation. Surg Clin N Am 1978;58:1313–22.
[12] Baxter CR, Marvin JA, Currieri PW. Early management of thermal burns. Postgraduate Med 1974;55:131–8.
[13] Engrav LH, Colescott PL, Kemalyan N, Heimbach DM, Gibran NS, Solem LD, et al. A biopsy of the use of the Baxter formula to resuscitate burns or do we do it like Charlie did it? J Burn Care Rehabil 2000;21:91–5.
[14] Pruitt Jr BA. Protection from excessive resuscitation: "pushing the pendulum back". J Trauma 2000;49:567–8.
[15] Biffl WL, Moore EE, Burch JM, Offner PJ, Franciose RJ, Johnson JL. Secondary abdominal compartment syndrome is a highly lethal event. Am J Surg 2001;182:645–8.
[16] Ivy ME, Atweh NA, Palmer J, Possenti PP, Pineau M, D'Aiuto M. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. J Trauma 2000;49:387–91.
[17] Hobson KG, Young KM, Ciraulo A, Palmieri TL, Greenhalgh DG. Release of abdominal compartment syndrome improves survival in patients with burn injury. J Trauma 2002;53:1129–33 (discussion 1133–4).
[18] Sheridan RL, Tompkins RG, McManus WF, Pruitt Jr BA. Intracompartmental sepsis in burn patients. J Trauma 1994;36:301–5.
[19] Kreimeier U. Pathophysiology of fluid imbalance. Crit Care 2000;4(Suppl 2):S3–7.
[20] Marks RM, Sachar EJ. Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med 1973;78:173–81.
[21] Choiniere M, Melzack R, Girard N, Rondeau J, Paquin MJ. Comparisons between patients' and nurses' assessment of pain and medication efficacy in severe burn injuries. Pain 1990;40:143–52.
[22] Melzack R. The tragedy of needless pain. Sci Am 1990;262:27–33.
[23] Ulmer JF. Burn pain management: a guideline-based approach. J Burn Care Rehabil 1998;19:151–9.
[24] Perry S, Heidrich G, Ramos E. Assessment of pain burn patients. J Burn Care Rehabil 1981;2:322–6.
[25] Heidrich G, Perry S, Amand R. Nursing staff attitudes about burn pain. J Burn Care Rehabil 1981;2:259–61.
[26] Friedrich JB, Sullivan SR, Engrav LH, Round KA, Blayney CB, Carrougher GJ, et al. Is supra-Baxter resuscitation in burn patients a new phenomenon? Burns, in press.
[27] Rouby JJ, Eurin B, Glaser P, Guillosson JJ, Nafziger J, Guesde R, et al. Hemodynamic and metabolic effects of morphine in the critically ill. Circulation 1981;64:53–9.
[28] Hedderich R, Ness TJ. Analgesia for trauma and burns. Crit Care Clin 1999;15:167–84.
[29] Kealey GP. Opioids and analgesia. J Burn Care Rehabil 1995;16: 363–4.
[30] Honari S, Patterson DR, Gibbons J, Martin-Herz SP, Mann R, Gibran NS, et al. Comparison of pain control medication in three age groups of elderly patients. J Burn Care Rehabil 1997;18:500–4.
[31] Max MB, Payne R. Principles of Analgesic Use in the Tratement of Acute Pain and Cancer Pain. Skokie, IL: American Pain Society; 1992.
[32] Gibbons J, Honari SR, Sharar SR, Patterson DR, Dimick PL, Heimbach DM. Opiate-induced respiratory depression in young pediatric burn patients. J Burn Care Rehabil 1998;19:225–9.
[33] Latarjet J, Choinere M. Pain in burn patients. Burns 1995;21:344–8.
[34] Walkenstein MD. Comparison of burned patients' perception of pain with nurses' preception of patients' pain. J Burn Care Rehabil 1982;3:233–9.
[35] Iafrati NS. Pain on the burn unit: patient vs. nurse perceptions. J Burn Care Rehabil 1986;7:413–6.
[36] Rae CP, Gallagher G, Watson S, Kinsella J. An audit of patient perception compared with medical and nursing staff estimation of pain during burn dressing changes. Eur J Anaesthesiol 2000;17:43–5.

[37] Byers JF, Bridges S, Kijek J, LaBorde P. Burn patients' pain and anxiety experiences. J Burn Care Rehabil 2001;22:144–9.
[38] Atchison NE, Osgood PF, Carr DB, Szyfelbein SK. Pain during burn dressing change in children: relationship to burn area, depth and analgesic regimens. Pain 1991;47:41–5.
[39] Luterman A, Curreri PW. Guidelines for early management of burn injuries. Drug Therapy 1980;December:15–26.
[40] Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman J, Limbird L, editor. Goodman & Gilman's the Pharmacological Basis of Therapeutics. New York: McGraw-Hill; 1996. p. 521–55.
[41] Jonsson CE, Holmsten A, Dahlstrom L, Jonsson K. Background pain in burn patients: routine measurement and recording of pain intensity in a burn unit. Burns 1998;24:448–54.
[42] Marvin JA, Heimbach DM. Pain control during the intensive care phase of burn care. Crit Care Clin 1985;1:147–57.
[43] Ashburn MA. Burn pain: the management of procedure-related pain. J Burn Care Rehabil 1995;16:365–71.
[44] Martyn J. Clinical pharmacology and drug therapy in the burned patient. Anesthesiology 1986;65:67–75.
[45] Jaehde U, Sorgel F. Clinical pharmacokinetics in patients with burns. Clin Pharmacokinet 1995;29:15–28.
[46] Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. Pain 1998;74:43–53.
[47] Herman RA, Veng-Pedersen P, Miotto J, Komorowski J, Kealey GP. Pharmacokinetics of morphine sulfate in patients with burns. J Burn Care Rehabil 1994;15:95–103.
[48] Furman WR, Munster AM, Cone EJ. Morphine pharmacokinetics during anesthesia and surgery in patients with burns. J Burn Care Rehabil 1990;11:391–4.
[49] Perry S, Inturrisi CE. Analgesia and morphine disposition in burn patients. J Burn Care Rehabil 1983;4:276–9.
[50] Perreault S, Choiniere M, du Souich PB, Bellavance F, Beauregard G. Pharmacokinetics of morphine and its glucuronidated metabolites in burn injuries. Ann Pharmacother 2001;35:1588–92.
[51] Patterson DR. Non-opioid-based approaches to burn pain. J Burn Care Rehabil 1995;16:372–6.
[52] Martyn JA, Abernethy DR, Greenblatt DJ. Plasma protein binding of drugs after severe burn injury. Clin Pharmacol Ther 1984;35:535–9.